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The Theory and Practice of Industrial Pharmacy

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11

Tablets

GILBERT S. BANKER *and* NEIL R. ANDERSON

Role in Therapy

The oral route of drug administration is the most important method of administering drugs for systemic effects. Except in cases of insulin therapy, the parenteral route is not routinely used for self-administration of medication. The topical route of administration has only recently been employed to deliver drugs to the body for systemic effects, with two classes of marketed products: nitroglycerin for the treatment of angina and scopolamine for the treatment of motion sickness. Other drugs are certain to follow, but the topical route of administration is limited in its ability to allow effective drug absorption for systemic drug action. The parenteral route of administration is important in treating medical emergencies in which a subject is comatose or cannot swallow, and in providing various types of maintenance therapy for hospitalized patients. Nevertheless, it is probable that at least 90% of all drugs used to produce systemic effects are administered by the oral route. When a new drug is discovered, one of the first questions a pharmaceutical company asks is whether or not the drug can be effectively administered for its intended effect by the oral route. If it cannot, the drug is primarily relegated to administration in a hospital setting or physician's office. If patient self-administration cannot be achieved, the sales of the drug constitute only a small fraction of what the market would be otherwise.

Of drugs that are administered orally, solid oral dosage forms represent the preferred class of product. The reasons for this preference are as follows.

Tablets and capsules represent unit dosage forms in which one usual dose of the drug has been accurately placed. By comparison, liquid oral dosage forms, such as syrups, suspensions, emulsions, solutions, and elixirs, are usually designed to contain one dose of medication in 5 to 30 ml. The patient is then asked to measure his or her own medication using a teaspoon, tablespoon, or other measuring device. Such dosage measurements are typically in error by a factor ranging from 20 to 50% when the drug is self-administered by the patient.

Liquid oral dosage forms have other disadvantages and limitations when compared with tablets. They are much more expensive to ship (one liquid dosage weighs 5 g or more versus 0.25 to 0.40 g for the average tablet), and breakage or leakage during shipment is a more serious problem with liquids than with tablets. Taste masking of the drug is often a problem (if the drug is in solution even partially). In addition, liquids are less portable and require much more space per number of doses on the pharmacist's shelf. Drugs are in general less stable (both chemically and physically) in liquid form than in a dry state and expiration dates tend to be shorter. Careful attention is required to assure that the product will not allow a heavy microbiologic burden to develop on standing or under normal conditions of use once opened (preservation requirements). There are basically three reasons for having liquid dosage forms of a drug: (1) The liquid form is what the public has come to expect for certain types of products (e.g., cough medicines). (2) The product is more effective in a liquid form (e.g., many adsorbents and antacids). (3) The drug(s) are used fairly commonly by young children or the elderly, who have trouble swallowing the solid oral dosage forms.

Advantages

Of the two oral solid dosage forms commonly employed in this country, the tablet and the capsule, the tablet has a number of advantages. One

of the major advantages of tablets over capsules, which has recently proved significant, is that the tablet is an essentially tamperproof dosage form. In recent episodes of tampering with pharmaceutical products, products have been altered after leaving the manufacturer and the wholesaler or distributor. A number of deaths and serious injuries have resulted from such tampering, with the result that the FDA has found it necessary to impose new standards for tamper-resistant packaging.[1] The major advantage of capsules—their ability to hide their contents from sight and to mask or hide the taste or odor of their contents—makes them the most vulnerable to tampering of all dosage forms. In contrast, any adulteration of a tablet after its manufacture is almost certain to be observed. Addition of any liquid to a tablet would produce disintegration if the liquid is aqueous, or would produce visible changes if the liquid is nonaqueous. Addition of extraneous powder to a tablet is not readily feasible. Even though improved packaging provides some consumer protection for such dosage forms as capsules, which are susceptible to tampering, *no* packaging is completely tamperproof.

A major disadvantage of capsules over tablets is their higher cost. Capsules, whether hard gelatin or soft elastic capsules, employ a capsule shell to contain the drug contents. The cost of this shell is approximately several tenths of a cent or more, depending on whether the capsule is banded, printed with identification, or otherwise treated. In addition to this is the cost of filling. This filling cost is higher than the typical total cost of tablet production, now that direct compression methods of tablet manufacture exist, since the capsule filling operation is far slower than the tablet compression operation.

In consideration of these few comparisons to capsules, the following may be cited as the primary potential advantages of tablets.

1. They are a unit dose form, and they offer the greatest capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
2. Their cost is lowest of all oral dosage forms.
3. They are the lightest and most compact of all oral dosage forms.
4. They are in general the easiest and cheapest to package and ship of all oral dosage forms.
5. Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.
6. They may provide the greatest ease of swallowing with the least tendency for "hang-up" above the stomach, especially when coated, provided that tablet disintegration is not excessively rapid.
7. They lend themselves to certain special-release profile products, such as enteric or delayed-release products.
8. They are better suited to large-scale production than other unit oral forms.
9. They have the best combined properties of chemical, mechanical and microbiologic stability of all the oral forms.

The development pharmacist should know fully what the potential advantages of tablets are as a dosage form class. If these general advantages together with the specific criteria specifications for the product are not met, an optimum or even near-optimum product may not have been achieved.

Disadvantages

The disadvantages of tablets include the following.

1. Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low-density character.

2. Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the gastrointestinal tract, or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate or full drug bioavailability.

3. Bitter-tasting drugs, drugs with an objectionable odor, or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment prior to compression (if feasible or practical), or the tablets may require coating. In such cases, the capsule may offer the best and lowest cost approach.

In summary of the foregoing advantages and disadvantages of tablets in comparison to other oral dosage forms, tablets do provide advantages to the pharmacist, in minimal storage space requirements as well as ease of dispensing and possibly control; to the patient in convenience of use, optimum portability, and lowest cost; and to the physician in flexibility of dosage (with bisected tablets), and in accuracy and precision of dosage in general.

Challenges in Product Design, Formulation, and Manufacture

As a class, tablets are one of the most challenging of all pharmaceutical products to design and manufacture. The difficulty of achieving full and reliable drug bioavailability for drugs with poor wetting and slow dissolution, for example, has previously been mentioned, as has the difficulty of achieving good cohesive compacts of amorphous or flocculent drugs. However, even for drugs with good compression characteristics, good dissolution, and no bioavailability problems, tablet product design and manufacture can be challenging because of the many competing objectives of this dosage form. That is, any action that is taken to improve one objective or set of objectives may cause another objective or set of objectives to degrade. For example, tablets should have a smooth surface, good appearance, and perhaps some surface gloss, and be cohesive and compact so that they do not undergo friability, powdering, or chipping in the bottle during shipping or handling. Whatever step is taken to achieve this first set of objectives, whether it is using more binder or adhesive, increasing compression pressure or punch dwell time, or using precompression, it may be expected to have a negative effect on another set of objectives, tablet disintegration time, drug dissolution rate, and possibly bioavailability. Depending on a drug's degree of compressibility, its dose, its solubility and solubility rate, its site of absorption along the GI tract, and other factors, finding a satisfactory compromise between competing sets of objectives may be simple or extremely complex.

When finding the correct compromise is not straightforward and simple, the pharmaceutical scientist should seriously consider use of optimization procedures to design the best compromise product.[2-4] Trial and error methods of formulation do not allow the formulator to know how close any particular formulation is to the optimum solution, and without a model to define the relationships between formulation and manufacturing variables, and levels of values for the quality features of the product, it is not possible to investigate play-off decisions between objectives. Once the product is mathematically/statistically modeled, one can compute how much a secondary objective or set of objectives suffers or gains if a primary objective specification is slightly relaxed (or tightened). As a result of the various competing objectives that are encountered in tablet product design, the formulation and manufacture of this product class are ideal for a mathematical optimization approach. Whether or not such an approach may be warranted depends on how simple and straightforward the design/manufacturing processes appear to be; however, using statistical experimental design procedures readily available today, the generation of a model for the system may be little additional work, if any, especially with computer assistance. It is preferable to stumbling through three or four levels of trial and error experimentation.

The Pharmaceutical Tablet Dosage Form

Properties

The objective of the design and manufacture of the compressed tablet is to deliver orally the correct amount of drug in the proper form, at or over the proper time and in the desired location, and to have its chemical integrity protected to that point. Aside from the physical and chemical properties of the medicinal agent(s) to be formulated into a tablet, the actual physical design, manufacturing process, and complete chemical makeup of the tablet can have a profound effect on the efficacy of the drug(s) being administered.

A tablet (1) should be an elegant product having its own identity while being free of defects such as chips, cracks, discoloration, contamination, and the like; (2) should have the strength to withstand the rigors of mechanical shocks encountered in its production, packaging, shipping, and dispensing; and (3) should have the chemical and physical stability to maintain its physical attributes over time. Pharmaceutical scientists now understand that various physical properties of tablets can undergo change under environmental or stress conditions, and that physical stability, through its effect on bioavailability in particular, can be of more significance and concern in some tablet systems than chemical stability.

On the other hand, the tablet (1) must be able to release the medicinal agent(s) in the body in a predictable and reproducible manner and (2) must have a suitable chemical stability over time so as not to allow alteration of the medicinal agent(s). In many instances, these sets of objectives are competing. The design of a tablet that emphasizes only the desired medicinal effects may produce a physically inadequate product. The design of a tablet emphasizing only the

physical aspects may produce tablets of limited and varying therapeutic effects. As one example of this point, Meyer and associates present information on 14 nitrofurantoin products, all of which passed the compendial physical requirements, but showed statistically significant bioavailability differences.[5]

Evaluation

To design tablets and later monitor tablet production quality, quantitative evaluations and assessments of a tablet's chemical, physical, and bioavailability properties must be made. Not only could all three property classes have a significant stability profile, but the stability profiles may be interrelated, i.e., *chemical* breakdown or interactions between tablet components may alter *physical* tablet properties, greatly changing the *bioavailability* of a tablet system.

General Appearance. The general appearance of a tablet, its visual identity and overall "elegance," is essential for consumer acceptance, for control of lot-to-lot uniformity and general tablet-to-tablet uniformity, and for monitoring trouble-free manufacturing. The control of the general appearance of a tablet involves the measurement of a number of attributes such as a tablet's size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws and consistency, and legibility of any identifying markings.

Size and Shape. The size and shape of the tablet can be dimensionally described, monitored, and controlled. A compressed tablet's shape and dimensions are determined by the tooling during the compression process. The thickness of a tablet is the only dimensional variable related to the process. At a constant compressive load, tablet thickness varies with changes in die fill, with particle size distribution and packing of the particle mix being compressed, and with tablet weight, while with a constant die fill, thickness varies with variations in compressive load. Tablet thickness is consistent batch to batch or within a batch only if the tablet granulation or powder blend is adequately consistent in particle size and size distribution, if the punch tooling is of consistent length, and if the tablet press is clean and in good working order.

The crown thickness of individual tablets may be measured with a micrometer, which permits accurate measurements and provides information on the variation between tablets. Other techniques employed in production control involve placing 5 or 10 tablets in a holding tray, where their total crown thickness may be measured with a sliding caliper scale. This method is much more rapid than measurement with a micrometer in providing an overall estimate of tablet thickness in production operations, but it does not as readily provide information on variability between tablets; however, if the punch and die tooling has been satisfactorily standardized and the tablet machine is functioning properly, this method is satisfactory for production work.

Tablet thickness should be controlled within a ±5% variation of a standard value. Any variation in tablet thickness within a particular lot of tablets or between manufacturer's lots should not be apparent to the unaided eye for consumer acceptance of the product. In addition, thickness must be controlled to facilitate packaging. Difficulties may be encountered in the use of unit dose and other types of packaging equipment if the volume of the material being packaged is not consistent. A secondary packaging problem with tablets of variable thickness relates to consistent fill levels of the same product container with a given number of dosage units.

The physical dimensions of the tablet, along with the density of the materials in the tablet formulation and their proportions, determine the weight of the tablet. The size and shape of the tablet can also influence the choice of tablet machine to use, the best particle size for the granulation, production lot sizes that can be made, the best type of tablet processing that can be used, packaging operations, and the cost to produce the tablet. The shape of the tablet alone can influence the choice of tablet machine used. Shaped tablets requiring "slotted punches" must be run at slower speeds than are possible with round tablets, using conventional punches. Because of the nonuniform forces involved within a tablet during compression, the more convex the tablet surface, the more likely it is to cause capping problems, forcing the use of a slower tablet machine or one with precompression capabilities.[6]

Unique Identification Markings. Pharmaceutical companies manufacturing tablets often use some type of unique markings on the tablet in addition to color, to aid in the rapid identification of their products. These markings utilize some form of embossing, engraving, or printing. A look into the product identification section of the current Physician's Desk Reference (PDR),[7] provides a quick reference to the multitude of marking variations, both artistic and informational, that can be produced.

The type of informational markings placed on a tablet usually includes the company name or symbol, a product code such as that from the National Drug Code (NDC) number, the product

name, or the product potency. In the future, these identifying marks, in conjunction with a greater diversity of tablet sizes and shapes, may provide the sole means of identification of tablets, if the pharmaceutical industry continues to lose the use of approved Food, Drug, and Cosmetic (FD&C) colors.

Organoleptic Properties. Many pharmaceutical tablets use color as a vital means of rapid identification and consumer acceptance. The color of a product must be uniform within a single tablet (nonuniformity is generally referred to as "mottling"), from tablet to tablet, and from lot to lot. Nonuniformity of coloring not only lacks esthetic appeal but could be associated by the consumer with nonuniformity of content and general poor quality of the product.[8]

The eye cannot discriminate small differences in color nor can it precisely define color. The eye has limited memory storage capability for color, and the storage of visually acquired data is difficult, which results in people perceiving the same color differently and a single person describing the same color differently at different times. In addition, visual color comparisons require that a sample be compared against some color standard. Color standards themselves are subject to change with time, thus forcing their frequent redefinition, which can lead to a gradual and significant change in acceptable color.[8] Efforts to quantitate color evaluations have used reflectance spectrophotometry, tristimulus colorimetric measurements, and the use of a microreflectance photometer to measure the color uniformity and gloss on a tablet surface.[8–10]

The presence of an odor in a batch of tablets could indicate a stability problem, such as the characteristic odor of acetic acid in degrading aspirin tablets; however, the presence of an odor could be characteristic of the drug, (vitamins have a characteristic odor), added ingredients (flavoring agents have pleasant odors), or the dosage form (film-coated tablets usually have a characteristic odor).

Taste is important in consumer acceptance of chewable tablets. Many companies utilize taste panels to judge the preference of different flavors and flavor levels in the development of a product. Owing to the subjectiveness of "taste" preference, however, the control of taste in the production of chewable tablets is often simply the presence or absence of a specified taste.

A tablet's level of flaws such as chips, cracks, contamination from foreign solid substances (e.g., hair, drops of oil, and "dirt"), surface texture ("smooth" versus "rough"), and appearance ("shiny" versus "dull") may have a zero-defect specification, but the visual inspection techniques used for detecting or evaluating these characteristics are subjective in nature. Electronic devices that are currently being developed hold promise for making inspection a more quantitative and reproducible operation.

Hardness and Friability. Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging, and shipping. In addition, tablets should be able to withstand reasonable abuse when in the hands of the consumer, such as bouncing about in a woman's purse in a partially filled prescription bottle. Adequate tablet hardness and resistance to powdering and friability are necessary requisites for consumer acceptance. More recently, the relationship of hardness to tablet disintegration, and perhaps more significantly, to the drug dissolution release rate, has become apparent. The monitoring of tablet hardness is especially important for drug products that possess real or potential bioavailability problems or that are sensitive to altered dissolution release profiles as a function of the compressive force employed.

Historically, the strength of a tablet was determined by breaking it between the second and third fingers with the thumb acting as a fulcrum. If there was a "sharp" snap, the tablet was deemed to have acceptable strength. More recently, however, tablet hardness has been defined as the force required to break a tablet in a diametric compression test. To perform this test, a tablet is placed between two anvils, force is applied to the anvils, and the crushing strength that just causes the tablet to break is recorded. Hardness is thus sometimes termed the *tablet crushing strength.* Several devices operating in this manner have been and continue to be used to test tablet hardness: the Monsanto tester, the Strong-Cobb tester, the Pfizer tester, the Erweka tester, and the Schleuniger tester.[11–15]

One of the earliest testers to evaluate tablet hardness was the Monsanto hardness tester, which was developed approximately fifty years ago. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet, and a zero reading is taken. The upper plunger is then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded, and the zero force reading is deducted from it. To overcome the manual nature of the Monsanto tester and the minute or longer time required to make an indi-

vidual test, the Strong-Cobb tester was developed about twenty years later. The original design employed a plunger activated by pumping a lever arm, which forces an anvil against a stationary platform by hydraulic pressure. The force required to fracture the tablet is read from a hydraulic gauge. Later modifications of the Strong-Cobb tester were built with the force applied by air-pressure rather than by a manual pump.

Approximately one decade later, the Pfizer tester was developed and made available to the industry. This tester operates on the same mechanical principle as a pair of pliers. As the plier's handles are squeezed, the tablet is compressed between a holding anvil and a piston connected to a direct force reading gauge. The dial indicator remains at the reading where the tablet breaks and is returned to zero by depressing a reset button. The Pfizer tester became extensively used in comparison to the earlier testers, based on its simplicity, low cost, and the rapidity with which it could be used.

Two testers have been developed to eliminate operator variation. In the Erweka tester, the tablet is placed on the lower anvil, and the anvil is then adjusted so that the tablet just touches the upper test anvil. A suspended weight, motor driven, moves along a rail, which slowly and uniformly transmits pressure to the tablet. A pointer moving along a scale provides the breaking strength value in kilograms. As shown in Figure 11-1, the Schleuniger tester operates in a horizontal position. An anvil driven by an electric motor presses the tablet at a constant load rate against a stationary anvil until the tablet breaks. A pointer moving along a scale indicator provides the breaking strength value. The instrument reads in both kilograms and Strong-Cobb units. This instrument is currently the most widely employed and has the advantage of being both fast and reproducible.

Unfortunately, these testers do not produce the same results for the same tablet. Studies have shown that operator variation, lack of calibration, spring fatigue, and manufacturer variation contribute greatly to the lack of uniformity. Even those testers designed to eliminate operator variability have been found to vary.[15,16]

Operators must be aware of these variations, especially when the tablets are to be evaluated by other persons or in other labs. For accurate comparison, each instrument should be carefully calibrated against a known standard.

The hardness of a tablet, like its thickness, is a function of the die fill and compression force. At a constant die fill, the hardness values increase and thickness decreases as additional compression force is applied. This relationship holds up to a maximum value for hardness and a mini-

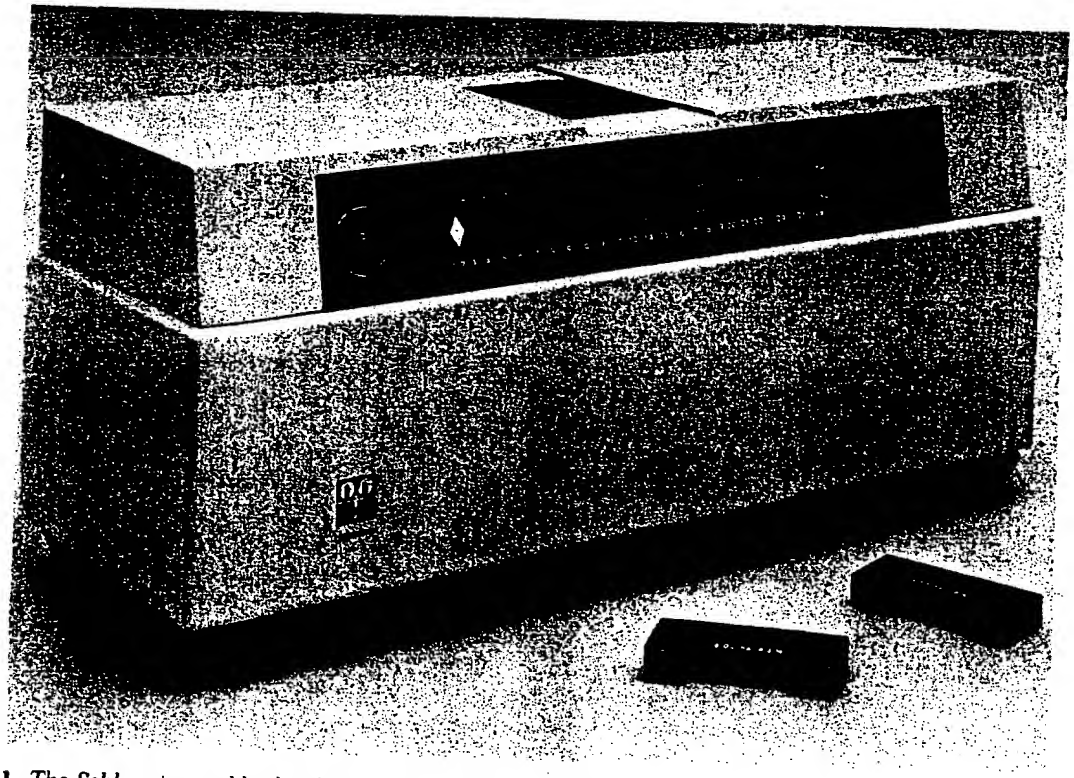

FIG. 11-1. *The Schleuniger tablet hardness tester. (Courtesy of Vector Corporation, Marion, IA.)*

mum value for thickness, beyond which increases in pressure cause the tablet to laminate or cap, thus destroying the integrity of the tablet. At a constant compression force (fixed distance between upper and lower punches), hardness increases with increasing die fills and decreases with lower die fills.

When uniform tooling is used, the die-fill/force relationship makes control of tablet hardness a useful method of physically controlling tablet properties during a production operation, particularly when this measurement is combined with measurements of tablet thickness. The fill/force relationship is also the basis for instrumenting tablet machines.

In general, tablets are harder several hours after compression than they are immediately after compression. Lubricants can affect tablet hardness when they are used in too high a concentration or mixed for too long a period. Large tablets require a greater force to cause fracture and are therefore "harder" than small tablets. For a given granulation, a flat beveled tool produces a tablet harder than a deep cup tool.

Tablet hardness is not an absolute indicator of strength since some formulations, when compressed into very hard tablets, tend to "cap" on attrition, losing their crown portions. Therefore, another measure of a tablet's strength, its friability, is often measured. Tablets that tend to powder, chip, and fragment when handled lack elegance and consumer acceptance, and can create excessively dirty processes in such areas of manufacturing as coating and packaging. They can also add to a tablet's weight variation or content uniformity problems.

The laboratory friability tester is known as the Roche friabilator.[17] This device, shown in Figure 11-2, subjects a number of tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm, dropping the tablets a distance of six inches with each revolution. Normally, a preweighed tablet sample is placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Conventional compressed tablets that lose less than 0.5 to 1.0% of their weight are generally considered acceptable. Some chewable tablets and most effervescent tablets undergo high friability weight losses, which accounts for the special stack packaging that may be required for these types of tablets. When capping is observed on friability testing, the tablet should not be considered for commercial use, regardless of the percentage of loss seen.

When concave and especially deep concave punches are used in tabletting, and especially

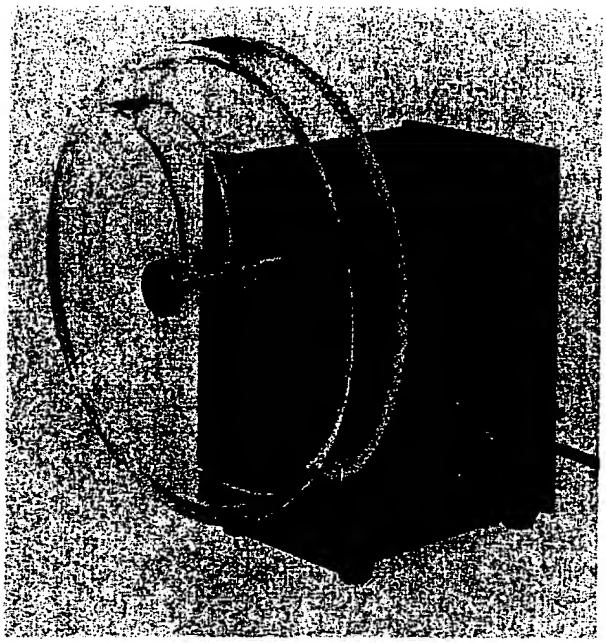

FIG. 11-2. *The Roche type friabilator. (Courtesy of Van-Kel Industries, Chatham, NJ.)*

when the punches are in poor condition or worn at their surface edges, the tablets produced result in "whiskering" at the tablet edge. Such tablets have higher than normal friability values because the "whiskers" are removed in testing. Tablet friability may also be influenced by the moisture content of the tablet granulation and finished tablets. A low but acceptable moisture level frequently acts as a binder. Very dry granulations that contain only fractional percentages of moisture often produce more friable tablets than do granulations containing 2 to 4% moisture. For this reason, the manufacture of chemically stable tablets that contain some hydrolyzable drugs that are mechanically sound is difficult.

The traditional hardness and friability evaluations performed on tablets involve only a small sample of tablets. How the tablets withstand the mechanical shocks of a production environment is related to the large number of tablets involved, the production equipment used, and the skill of the production personnel. Rough handling tests can be performed to give an indication of how well a tablet will hold up in its specified package and shipping container during shipment. Rough handling tests usually include a vibration test, a drop test, and an incline plane impact test.[18] Some investigators have actually shipped bottled products across the country and back again to estimate the strength of the new tablet product in shipment.

Drug Content and Release. As mentioned

earlier, a physically sound tablet may not produce the desired effects. To evaluate a tablet's potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet and batch to batch, and a measure of the tablet's ability to release the drug needs to be ascertained.

Weight Variation. With a tablet designed to contain a specific amount of drug in a specific amount of tablet formula, the weight of the tablet being made is routinely measured to help ensure that a tablet contains the proper amount of drug. In practice, composite samples of tablets (usually 10) are taken and weighed throughout the compression process. The composite weight divided by 10, however, provides an average weight but contains the usual problems of averaged values. Within the composite sample that has an acceptable average weight, there could be tablets excessively overweight or underweight. To help alleviate this problem the United States Pharmacopeia (USP)/National Formulary (NF) provides limits for the permissible variations in the weights of individual tablets expressed as a percentage of the average weight of the sample.[19] The USP weight variation test is run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. The weight variation tolerances for uncoated tablets differ depending on average tablet weight (Table 11-1).

The weight variation test would be a satisfactory method of determining the drug content uniformity of tablets if the tablets were all or essentially all (90 to 95%) active ingredient, or if the uniformity of the drug distribution in the granulation or powder from which the tablets were made were perfect. For tablets such as aspirin, which are usually 90% or more active ingredient, the ±5% weight variation should come close to defining true potency and content uniformity (95 to 105% of the label strength) if the average tablet weight is close to the theoretic average weight. The weight variation test is clearly not sufficient to assure uniform potency of tablets of moderate- or low-dose drugs, in which excipients make up the bulk of the tablet weight.

TABLE 11-1. *Weight Variation Tolerances for Uncoated Tablets*

Average Weight of Tablets (mg)	*Maximum Percentage Difference Allowed*
130 or less	10
130–324	7.5
More than 324	5

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The potency of tablets is expressed in terms of grams, milligrams, or micrograms (for some potent drugs) of drug per tablet and is given as the label strength of the product. Official compendia or other standards provide an acceptable potency range around the label potency. For highly potent, low-dose drugs such as digitoxin, this range is usually not less than 90% and not more than 110% of the labeled amount. For most other larger-dose drugs in tablet form, the official potency range that is permitted is not less than 95% and not more than 105% of the labeled amount.

In general, official potency analytic methods require that a composite sample of the tablets be taken, ground up, mixed, and analyzed to produce an average potency value. In composite assays, individual discrepancies can be masked by use of the blended sample. Even though the average assay result looks acceptable, it could mask a wide variation in potency, with the result that a patient could be variably underdosed or overdosed. With such a drug as digitoxin, in which the safe and effective level and the toxic level are close (or even overlapping), exceeding the official or accepted potency range is not only undesirable, but possibly dangerous.

Three factors can directly contribute to content uniformity problems in tablets: (1) nonuniform distribution of the drug substance throughout the powder mixture or granulation, (2) segregation of the powder mixture or granulation during the various manufacturing processes, and (3) tablet weight variation. As noted in the previous section, the use of weight cannot be used as a potency indicator, except perhaps when the active ingredient is 90 to 95% of the total tablet weight. In tablets with smaller dosages, a good weight variation does not ensure good content uniformity, but a large weight variation precludes good content uniformity.

To assure uniform potency for tablets of low-dose drugs, a content uniformity test is applied.[19] In this test, 30 tablets are randomly selected for the sample, and at least 10 of them are assayed individually. Nine of the 10 tablets must contain not less than 85% or more than 115% of the labeled drug content. The tenth tablet may not contain less than 75% or more than 125% of the labeled content. If these conditions are not met, the tablets remaining from the 30 must be assayed individually, and none may fall outside

of the 85 to 115% range. In evaluating a particular lot of tablets, several samples of tablets should be taken from various parts of the production run to satisfy statistical procedures.

The *purity* of official tablets is usually assured by utilizing raw materials, both active drug and all excipients, that meet official or other rigid specifications. Extraneous substances present in a raw material or a drug that are not specifically allowed by compendial specifications or well-defined manufacturer's specifications may render the product unacceptable for pharmaceutical use. These extraneous substances may be toxic on acute or long-term use or may have an unpredictable or deleterious effect on product stability or efficacy. Certain well-defined impurities often appear in the specification of raw materials or drug substances, or if they are the product of unavoidable decomposition of the drug, they may be listed with an upper tolerance limit. For example, aspirin tablets as specified by the USP may contain no more than 0.15% of free salicylic acid relative to the amount of aspirin present.

Disintegration. A generally accepted maxim is that for a drug to be readily available to the body, it must be in solution. For most tablets, the first important step toward solution is breakdown of the tablet into smaller particles or granules, a process known as *disintegration*. The time that it takes a tablet to disintegrate is measured in a device described in the USP/NF.[19] Wagner has written an excellent review of the disintegration test,[20] to which the reader is referred for a more detailed study.

Research has established that one should not automatically expect a correlation between disintegration and dissolution. However, since the dissolution of a drug from the fragmented tablet appears to control partially or completely the appearance of the drug in the blood, disintegration is still used as a guide to the formulator in the preparation of an optimum tablet formula and as an in-process control test to ensure lot-to-lot uniformity.

The USP device to test disintegration uses 6 glass tubes that are 3 inches long, open at the top, and held against a 10-mesh screen at the bottom end of the basket rack assembly (Fig. 11-3). To test for disintegration time, one tablet is placed in each tube, and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid, or simulated intestinal fluid, at 37°C ± 2°C, such that the tablets remain 2.5 cm below the surface of the liquid on their upward movement and descend not closer than 2.5 cm from the bottom of the beaker. A standard motor-driven device is used to move the basket assembly containing the tablets up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute. Perforated plastic discs may also be used in the test. These are placed on top of the tablets and impart an abrasive action to the tablets. The discs may or may not be meaningful or impart more sensitivity to the test, but they are useful for tablets that float.

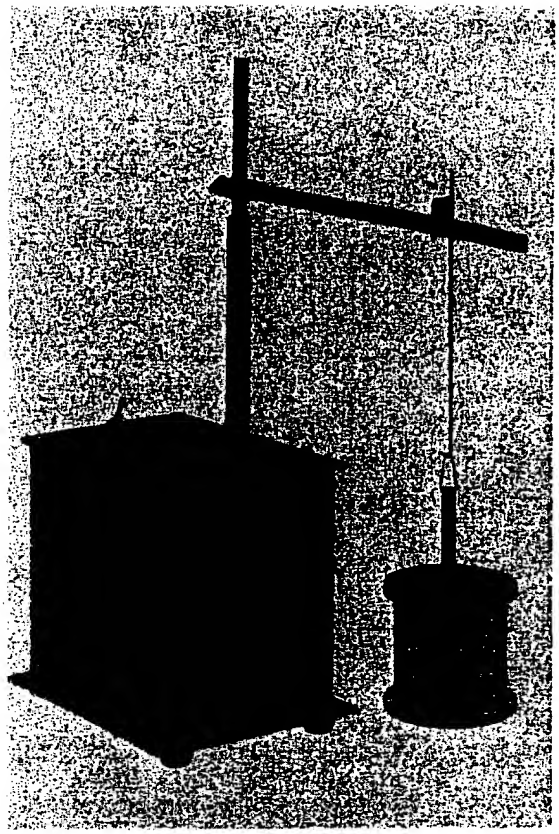

FIG. 11-3. *Tablet disintegration tester. (Courtesy of Van-Kel Industries, Chatham, NJ.)*

To be in compliance with the USP standards, the tablets must disintegrate, and all particles must pass through the 10-mesh screen in the time specified. If any residue remains, it must have a soft mass with no palpably firm core. Procedures are stated for running disintegration times for uncoated tablets, plain-coated tablets, enteric coated tablets, buccal tablets, and sublingual tablets. Uncoated USP tablets have disintegration time standards as low as 5 min (aspirin tablets), but the majority of the tablets have a maximum disintegration time of 30 min. Enteric coated tablets are to show no evidence of disintegration after 1 hour in simulated gastric fluid. The same tablets are then tested in simulated intestinal fluid and are to disintegrate in 2 hours plus the time specified in the monograph.

Dissolution. The original rationale for using tablet disintegration tests was the fact that as

the tablet breaks down into small particles, it offers a greater surface area to the dissolving media and therefore must be related to the availability of the drug to the body. The disintegration test, however, simply identifies the times required for the tablet to break up under the conditions of the test and for all particles to pass through a 10-mesh screen. The test offers no assurance that the resultant particles will release the drug in solution at an appropriate rate. For this reason, dissolution tests and test specifications have now been developed for nearly all tablet products. The rate of drug absorption for acidic drug moieties that are absorbed high in the GI tract is often determined by the rate of drug dissolution from the tablet. If the attainment of high peak blood levels for the drug is a product objective, obtaining rapid drug dissolution from the tablet is usually critically important. The rate of dissolution may thus be directly related to the efficacy of the tablet product, as well as to bioavailability differences between formulations. Therefore, an evaluation as to whether or not a tablet releases its drug contents when placed in the environment of the gastrointestinal tract is often of fundamental concern to the tablet formulator.

The most direct assessment of a drug's release from various tablet formulations or products is accomplished through in vivo bioavailability measurements. The use of in vivo studies is restricted, however, for several reasons: the length of time needed to plan, conduct, and interpret the study; the highly skilled personnel required for human studies; the low precision and high variability typical of the measurements; the high cost of the studies; the use of human subjects for "nonessential" research; and the necessary assumption that a perfect correlation exists between diseased patients and the healthy human subjects used in the test. Consequently, in vitro dissolution tests have been extensively studied, developed, and used as an indirect measurement of drug availability, especially in preliminary assessments of formulation factors and manufacturing methods that are likely to influence bioavailability. As with any in vitro test, it is critically important that the dissolution test be correlated with in vivo bioavailability tests.

Two objectives in the development of in vitro dissolution tests are to show (1) that the release of the drug from the tablet is as close as possible to 100% and (2) that the rate of drug release is uniform batch to batch and is the same as the release rate from those batches proven to be bioavailable and clinically effective. Since 1970, the United States Pharmacopeia and the National Formulary have provided procedures for dissolution testing. They determine compliance with the limits on dissolution as specified in the individual monograph for a tablet (or a capsule). The USPXX/NFXV, Supplement 3, specifies that either of two apparatuses be used for determining dissolution rates.[21]

Apparatus 1. In general, a single tablet is placed in a small wire mesh basket fastened to the bottom of the shaft connected to a variable speed motor (Fig. 11-4A). The basket is immersed in the dissolution medium (as specified in the monograph) contained in a 100-ml flask. The flask is cylindric with a hemispherical bottom. The flask is maintained at 37°C ± 0.5°C by a constant temperature bath. The motor is adjusted to turn at the specified speed, and samples of the fluid are withdrawn at intervals to determine the amount of drug in solution.

Apparatus 2. The same equipment as in apparatus 1 is used, except that the basket is replaced by a paddle, formed from a blade and a shaft, as the stirring element (Fig.4B). The dosage form is allowed to sink to the bottom of the flask before stirring. Dosage forms may have a "small, loose piece of nonreactive material such as not more than a few turns of wire helix" attached to prevent them from floating.[20] Description of a dissolution test in a USP/NF monograph specifies the dissolution test medium and volume, which apparatus is to be used, the speed (rpm) at which the test is to be performed, the time limit of the test, and the assay procedure. The test tolerance is expressed as a percentage of the labeled amount of drug dissolved in the time limit. For example, for methyldopa tablets, the dissolution test calls for a medium of 900 ml of 0.1N HCl, apparatus 2 turning at 50 rpm, and a time limit of 20 min. The accepted amount dissolved in 20 min is not less than 80% of the labeled amount of methyldopa (based on the cited assay procedure).

Dissolution testing and interpretation can be continued through three stages if necessary. In stage 1(S_1), six tablets are tested and are acceptable if all of the tablets are not less than the monograph tolerance limit (Q) plus 5%. If the tablets fail S_1, an additional six tablets are tested (S_2). The tablets are acceptable if the average of the twelve tablets is greater than or equal to Q and no unit is less than Q minus 15%. If the tablets still fail the test, an additional 12 tablets are tested. The tablets are acceptable if the average of all 24 tablets is greater than or equal to Q and if not more than 2 tablets are less than Q minus 15%.

Industrial pharmacists routinely test their formulations for dissolution. Their results are plotted as concentration versus time. Values for

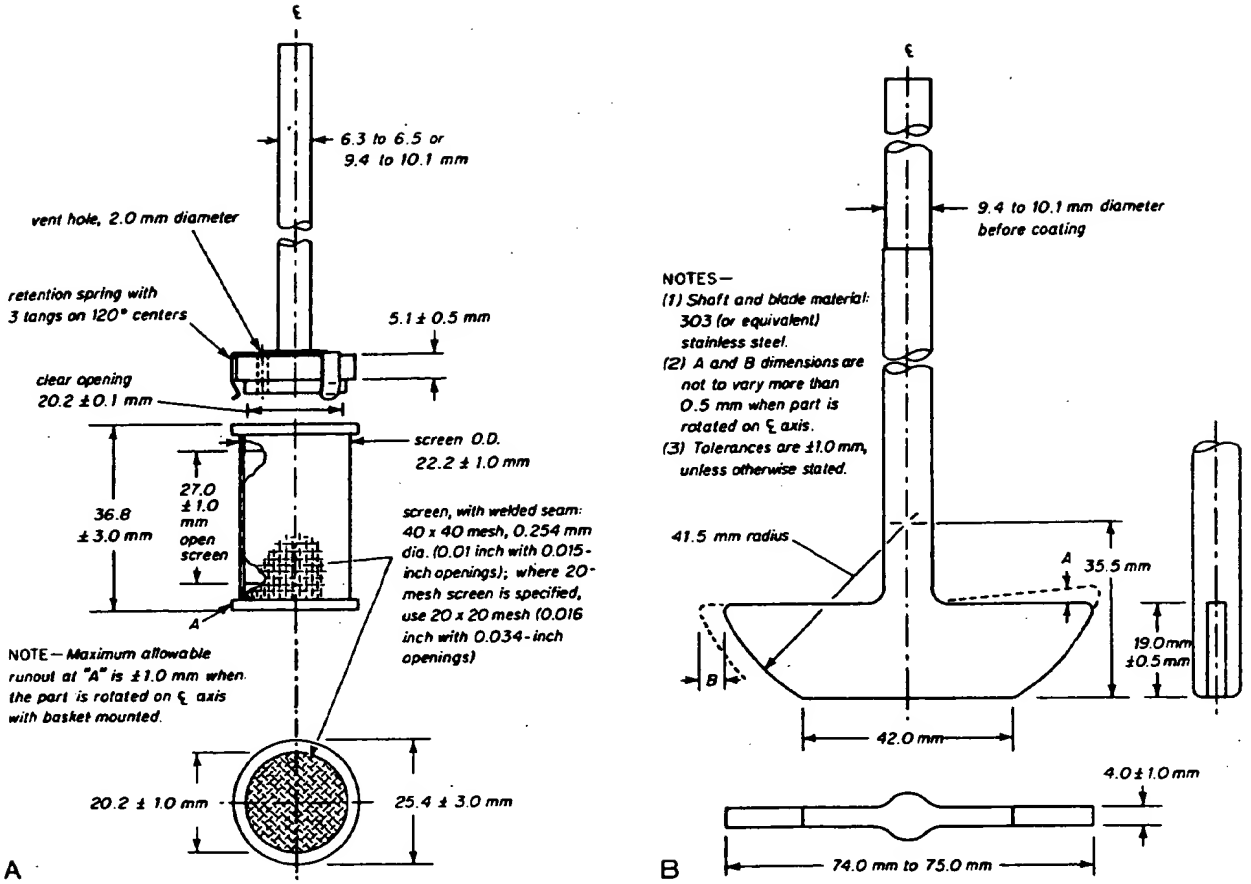

FIG. 11-4. A, *USP dissolution apparatus 1.* B, *USP dissolution apparatus 2. (Reproduced from the Third Supplement to USP XX-NF XV, © 1982, USP Convention, pages 310 and 311. Permission granted.)*

$t_{50\%}$, $t_{90\%}$, and the percentage dissolved in 30 min are used as guides. The value for $t_{50\%}$ is the length of time required for 50% of the drug to go into solution. A value for $t_{90\%}$ of 30 min is often considered satisfactory and is an excellent goal since a common dissolution tolerance in the USP/NF is not less than 75% dissolved in 45 min.

Tablet Compression Operation

Tablet Compression Machines

Tablets are made by compressing a formulation containing a drug or drugs with excipients on stamping machines called *presses.* Tablet compression machines or tablet presses are designed with the following basic components:

1. Hopper(s) for holding and feeding granulation to be compressed.
2. Dies that define the size and shape of the tablet.
3. Punches for compressing the granulation within the dies.
4. Cam tracks for guiding the movement of the punches.
5. A feeding mechanism for moving granulation from the hopper into the dies.

Tablet presses are classified as either single-punch or multi-station rotary presses. Figure 11-5 illustrates in cross-section the compression process on a single punch machine. Note that all of the compression is applied by the upper punch, making the single punch machine a "stamping press."

Multi-station presses are termed *rotary* because the head of the tablet machine that holds the upper punches, dies, and lower punches in place rotates. As the head rotates, the punches are guided up and down by fixed cam tracks, which control the sequence of filling, compression, and ejection. The portions of the head that hold the upper and lower punches are called the upper and lower turrets respectively, and the

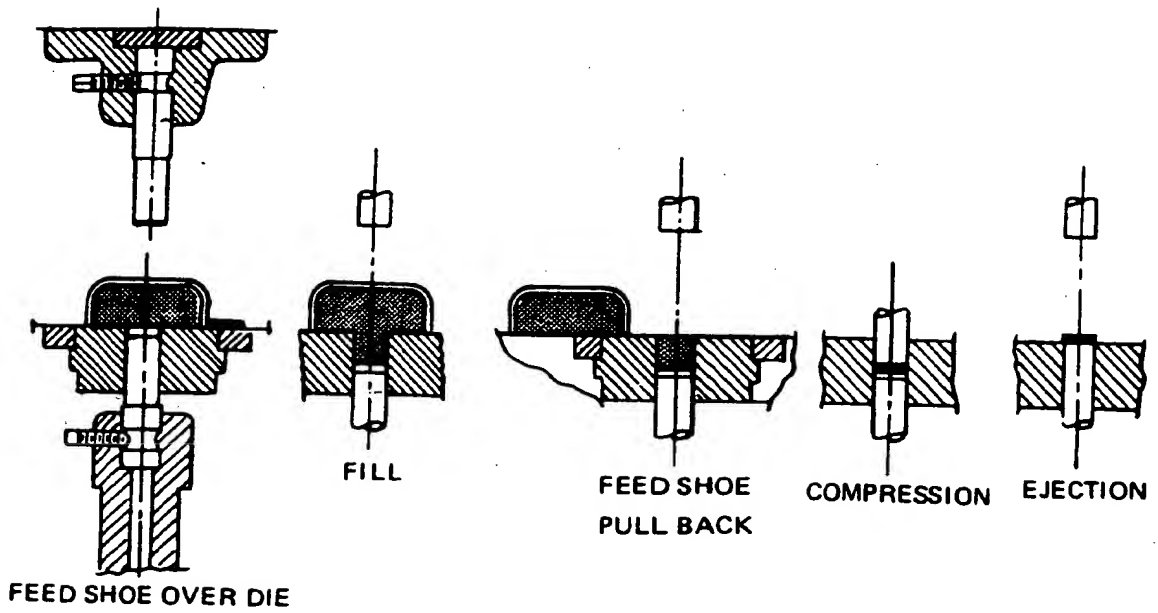

FIG. 11-5. *The compression cycle of a single-punch tablet press. (Courtesy of Vector Corporation, Marion, IA.)*

portion holding the dies is called the *die table*. At the start of a compression cycle (Fig. 11-6), granulation stored in a hopper (not shown), empties into the feed-frame (A), which has several interconnected compartments (Fig. 11-7). These compartments spread the granulation over a wide area to provide time for the dies (B) to fill (Fig. 11-6). The pull-down cam (C) of Figure 11-6 guides the lower punches to the bottom of their vertical travel, allowing the dies to overfill. The punches then pass over a weight-control cam (E), which reduces the fill in the dies to the desired amount. A wipe-off blade (D) at the end of the feed-frame removes the excess granulation and directs it around the turret and back into the front of the feed-frame. Next, the lower punches travel over the lower compression roll (F) while simultaneously the upper punches ride beneath the upper compression roll (G). The upper punches enter a fixed distance into the dies, while the lower punches are raised to squeeze and compact the granulation within the dies. To regulate the upward movement of the lower punches, the height of the lower pressure roll is changed. After the moment of compression, the upper punches are withdrawn as they follow the upper punch raising cam (H); the lower punches ride up the cam (I), which brings the tablets flush with or slightly above the surface of the dies. The exact position is determined by a threaded bolt called the *ejector knob*. The tablets strike a sweep-off blade affixed to the front of the feed-frame (A) and slide down a chute into a receptacle. At the same time, the lower punches re-enter the pulldown cam (C), and the cycle is repeated.

Many production tablet machines are designed so that the compression cycle is accomplished more than once (requiring additional granulation hoppers, feed frames, cam tracks, and compression rolls) while the machine head makes a single revolution.

All other parts of a tablet press are designed to control the functioning of the components just listed. Such features as capacity, speed, maximum weight, and pressure vary with the design of the equipment, but the basic elements remain essentially the same.

Although tablet compressing machinery has undergone numerous mechanical modifications over the years, the compaction of materials between a pair of moving punches within a stationary die has remained unchanged. The principal modification from earlier equipment has been an increase in production rate rather than any fundamental change in the process. Better control and simplification have been corollary benefits.

In recent years, there has been a change by manufacturers from activities concerned with production rate to problems of process improvement and control. Growth of governmental and pharmacopeia tests related to intertablet weight and potency variation, as noted earlier in the chapter, have created some of the new requirements for tablet compressing machinery. As tablet production rates have increased with modern equipment, for example, the need for automatic

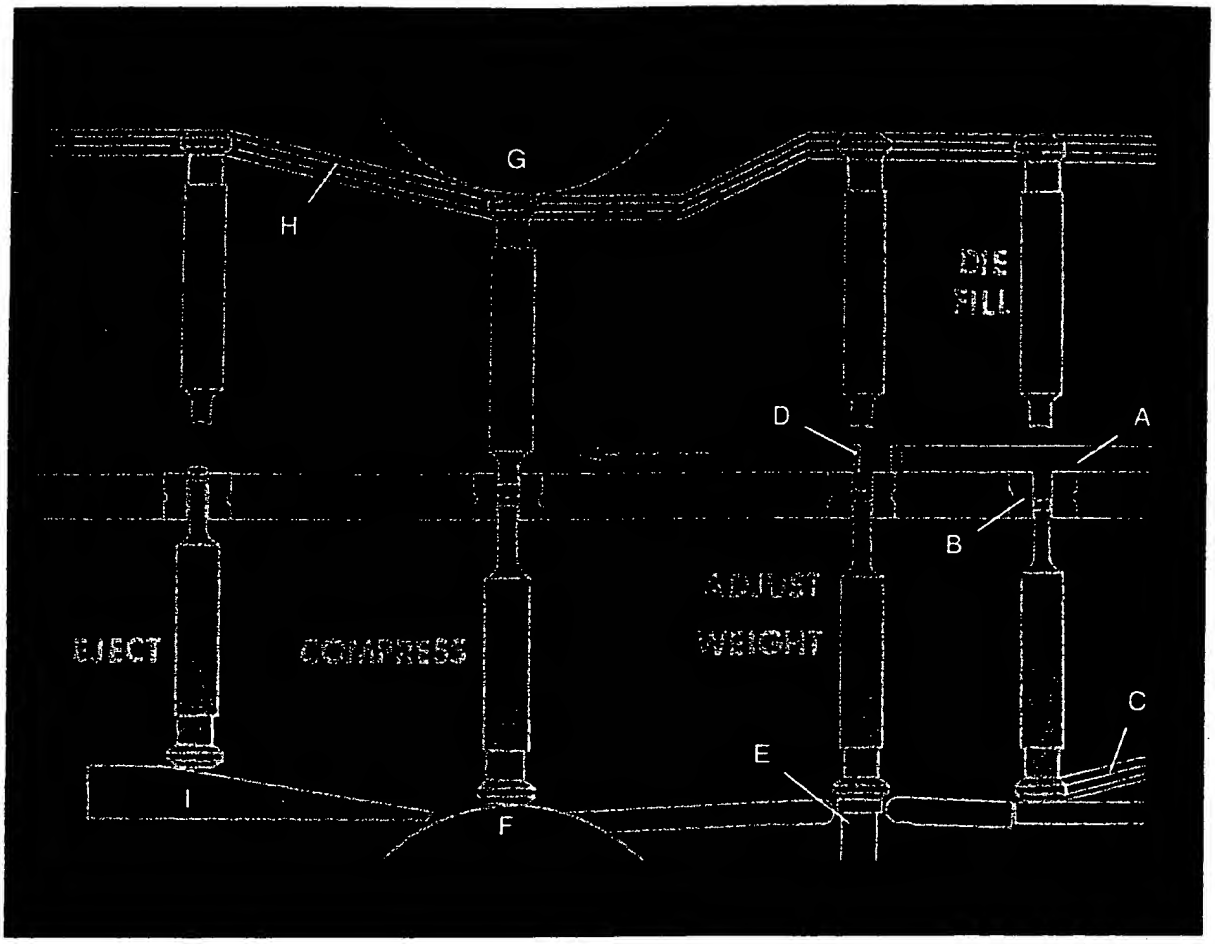

FIG. 11-6. *The compression cycle of a rotary tablet press. (See text for explanation of lettered labels.) (Courtesy of Thomas Engineering, Hoffman Estates, IL.)*

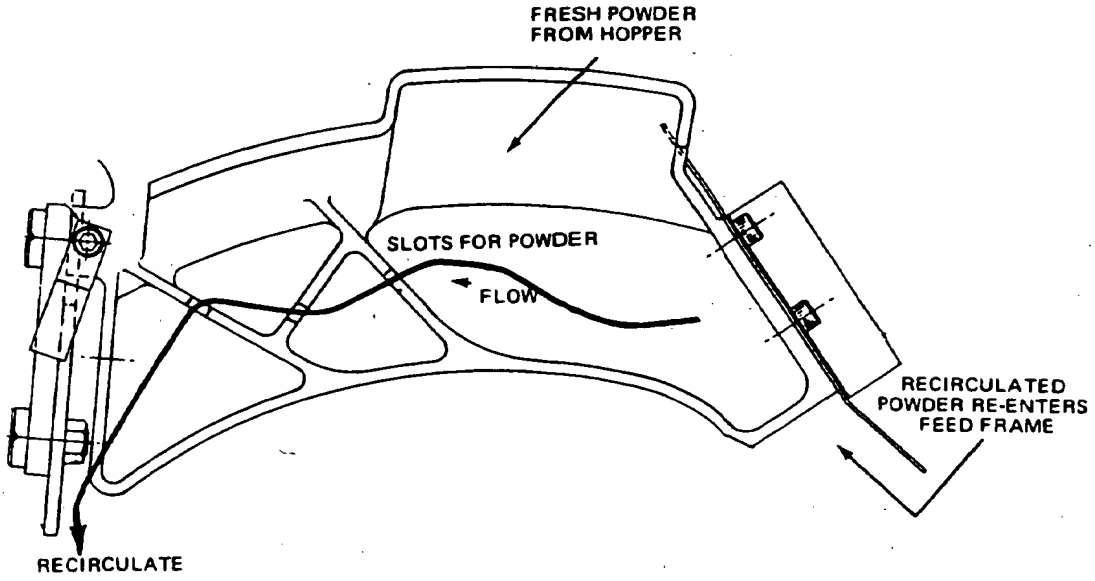

FIG. 11-7. *Granulation flow in an open feed frame of a rotary tablet press. (Courtesy of Vector Corporation, Marion, IA.)*

tablet weight control independent of operator vigilance has become a matter of increasing concern. This topic is discussed later, in the section "Auxiliary Equipment."

Tabletting presses vary principally in the number of tooling stations available for compression and in special application features. Table 11-2 tabulates the maximum and minimum tablet manufacturing output capable within the various press models of several manufacturers.

A tablet machine's output is regulated by three basic characteristics of its design:

Number of tooling sets

Number of compression stations

Rotational speed of the press

In general, all rotary presses are engineered for fast and economical production of all kinds of tablets. Larger machines can readily produce several million tablets each in a working day, and their performance can be geared to continuous low-maintenance operation. Figure 11-8 is an example of a modern high-speed tabletting machine.

There are many modifications and options that can be obtained from various manufacturers. One modification, which is found on most modern high-speed tablet presses, is the use of hydraulic or pneumatic pressure to control the pressure rolls in place of the older spring type pressure. Either of these alternatives gives a smoother pressure or compressive load force over a longer period of time. Hydraulic or pneumatic pressure is much more accurate and can be set with closer tolerances, which do not change with time or fatigue.

Special adaptations of tablet machines allow for the compression of "layered" tablets and coated tablets. Precompression stations are also available to help in compressing difficult granulations. Available with certain Fette machines is a device that chills the compression components to allow for the compression of low-melting-point substances such as waxes, thereby making it possible to compress products with low melting points, such as suppositories.

There are many basic and optional features available in tablet machines, including some not mentioned in this text. Manufacturers' brochures should be closely checked for available features. One should attend equipment shows, if possible, to obtain up-to-date information on equipment developments. In some instances, test runs on machinery may be made before a final decision to purchase new high-speed tablet equipment or specialized granulation or drying equipment.

Compression Machine Tooling

As mentioned earlier, the size and shape of a tablet as well as certain identification markings

TABLE 11-2. *Selected Rotary Tablet Press Characteristics*

Manufacturer	*Number of Stations Available*		*Rated Output, Tablets per Minute (TPM)*		*U.S. Representative*
	Min	*Max*	*Min*	*Max*	
Colton	12	90	480	16,000	Vector Corp. Marion, IA 52302
Wilhelm Fette, Gmbh Hamburg, W. Germany	20	55	300/900	3300/8250	Raymond Automation Company, Inc. Norwalk, CT 06856
Kilian & Co., Gmbh Koln, W. Germany	14	67	140/383	1083/10,000	INPPEC Fairfield, CT 06430
Manesty Machines Ltd. Liverpool, England	16	69	600/1500	3330/10,000	Thomas Engineering Hoffman Estates, IL 60172
Stokes-Merrill	33	65	1200/3300	3500/10,000	Stokes-Merrill Division Penwalt Corp. Oak Brook, IL 60521
Korsch Maschinenfabrik Berlin, W. Germany	20	55	540/1100	1640/5500	Aeromatic East Towaco, NJ 07082
Hata Ironworks Hori Engineering Co., Osaka, Japan	28	71	420/1420	1960/7100	Elizabeth-Hata International Inc. McKeesport, PA 15132

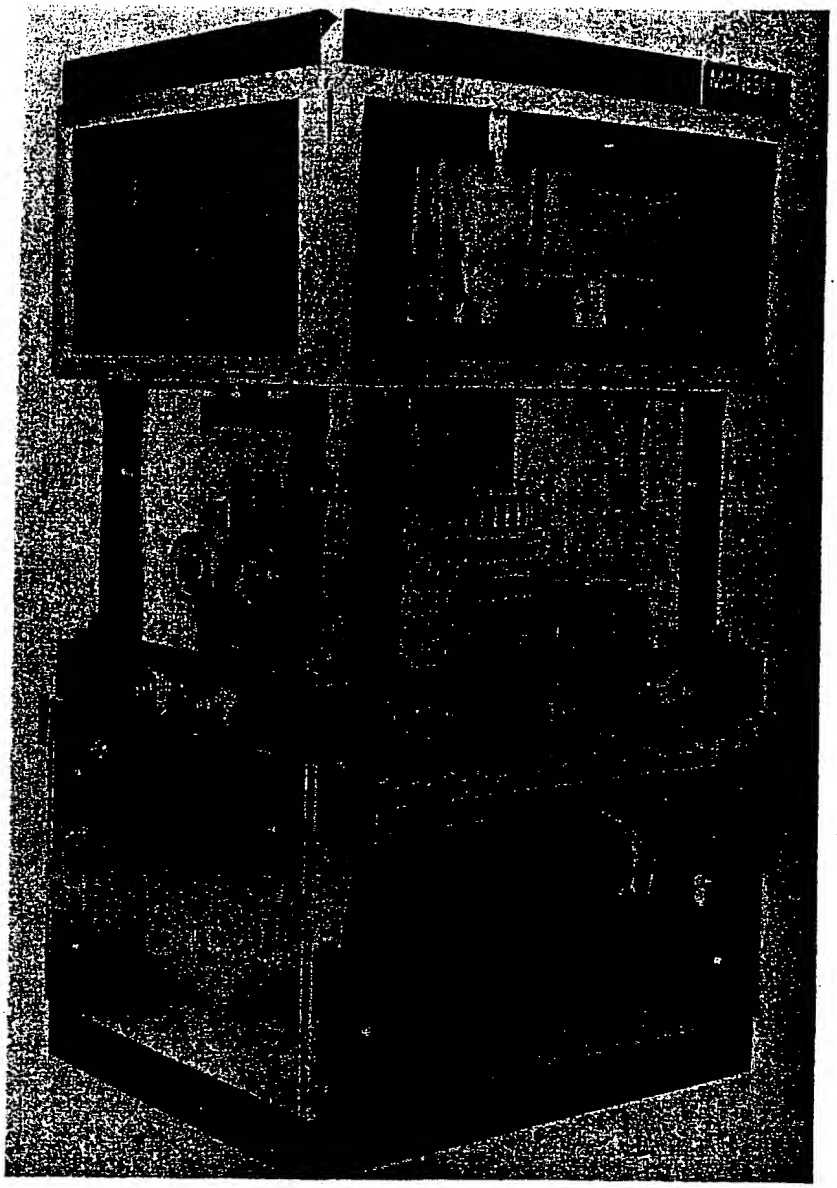

FIG. 11-8. *The Manesty Nova rotary tablet press. (Courtesy of Thomas Engineering, Hoffman Estates, IL.)*

are determined by the compression machine tooling. Each tooling set consists of a die and upper and lower punches. Since each tablet is formed by a tooling set, the tooling must meet many requirements to satisfy the needs of dosage uniformity, production efficiency, and esthetic appearance.

The terminology used with tooling is illustrated in Figure 11-9. The most common tools employed are referred to as BB tooling and are 5.25 inches in length, and have a nominal barrel diameter of 0.75 inches and 1-inch head diameter. B tooling is identical to the BB type except that the lower punch is only 3⁹⁄₁₆ inches long. D tooling is popular for large tablets, utilizing a 1-inch barrel diameter, 1¼-inch head diameter, and 5.25-inch length. The dies that are used with the above punches are either a 0.945-inch outside diameter (OD) die capable of making a ⁷⁄₁₆-inch round tablet or ⁹⁄₁₆-inch capsule-shaped tablet; or a 1³⁄₁₆-inch OD die capable of handling a ⁹⁄₁₆-inch round or ¾-inch capsule shaped tablet.

Several types of steel are normally used in the manufacture of compression tooling. These steels differ in toughness, to withstand the cyclic compacting forces (ductility), and in wear resistance. Unfortunately, no single steel type has a high resistance to abrasive wear and a high ductility. Therefore, the selection of the

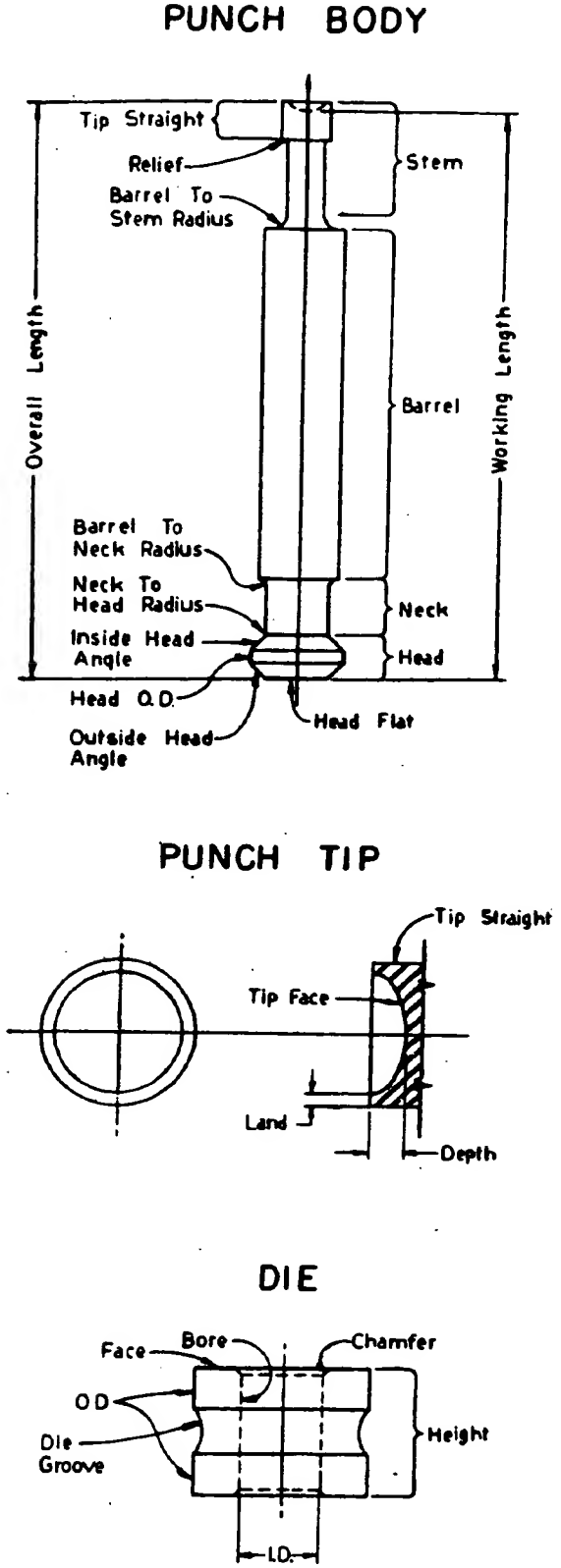

FIG. 11-9. *Tablet press tooling nomenclature. (Courtesy of Thomas Engineering, Hoffman Estates, IL.)*

best steel for a specific application must be based on experience and an accumulated history of the product being tabletted. In the selection of the proper steel for a specific use, one should also consider the shape of the punch tip, whether or not debossing is to be employed on the tooling, the expected compression forces involved, and whether the materials to be processed are abrasive or corrosive.

The size, shape, and contour of a tablet is almost unlimited within the given limits of the specified die size. A survey of the PDR Product Identification section reveals numerous variations on tablet size and shape.[4] In addition, tooling can be made with certain other information to aid in producing a visibly unique tablet product. Company names or symbols, trade names, dosage strength, or National Drug Code (NDC) numbers can be cut or engraved into a punch face, or the punches may be scored, to produce uniquely embossed or engraved tablets. Even though tooling design would appear to be limitless, certain practical aspects do limit design implementation. Because of the movement of tooling during a compression operation, certain tablet shapes or contour configurations perform better than others. Round tablets perform better than irregularly shaped tooling since they do not require "keying" to maintain the proper upper punch orientation with the die. When the tip on an upper punch is not round, it must not rotate, or it will strike the edge of the die hole as it descends for compression. To prevent this, a slot is cut longitudinally into the barrel of the punch, and a key is inserted. This key protrudes a short distance so that it engages a similar slot cut into the upper punch guides on the tablet press. Lower punches do not need keys because their tips remain within the die bore, which controls the axial movement of the punch. Because keyed punches cannot rotate, wear is distributed unevenly, and punch life is shortened.

When a press is set up with keyed punches, the upper punches are inserted first to determine the placement of the dies. Once the dies are properly aligned and seated, they are locked in place, and the lower punches are inserted. The more curvature that is built into a tablet contour, the more difficult it is to compress, especially if the tablet tends to laminate or cap. The engraving or embossing on a tablet must be designed to be legible, must not add to compression problems, and must fit on the tablet surface. Many considerations, at close tolerances, must be incorporated in tooling design to produce tablets that are uniform and esthetic. Manufacturing specifications for tooling have been standardized by the Industrial Pharmaceutical

Technology Section of the Academy of Pharmaceutical Sciences in its Standard Specifications of Tabletting Tools.[22]

Because of its hard steel structure, tablet tooling may appear to be indestructible. During normal use, however, the punches and dies become worn, and the cyclic application of stress can cause the steel to fatigue and break. Improper storage and handling can readily result in damage that necessitates discarding of an entire tooling set. The punch tips are especially delicate and susceptible to damage if the tips make contact with each other, the dies, or the press turret upon insertion or removal of the tools from the tablet machine. A good tool control system must be employed to maintain the history of each tool set, not only to maintain a constant surveillance of critical tolerances altered by wear, but also to eliminate product mixups by preventing the wrong tooling from being used for a product.

To avoid tooling damage, compressive loads or pressures at the pressure rolls must be translated into a calculation of pressure at the punch tips. As tablet punch diameter decreases, less force is required to produce the same pressure at the punch face, since the face represents a smaller fraction of a unit area (square inch). The formula for the area of a circle is πr^2 where r is the radius of the circle. Given a flat punch face, the area of a ¼-inch-diameter punch would thus be $3.14 \times (1/8)^2$ or $3.14 \times 1/64$, or approximately 1/20 square-inch. If a 1-ton load is being applied by the pressure roll, this area is translated as 2000 pounds on 1/20 square inch, or 40,000 pounds on 1 square inch, a gross overload.

The following are manufacturers of tablet compression tooling:

Thomas Engineering, Hoffman Estates, IL

Stokes, Warminster, PA

Natoli Engineering Company, Chesterfield, MO

Elizabeth Carbide Die Co., McKeesport, PA

Key Industries, Englishtown, NJ

Advance Engineering and Manufacturing Co., St. Louis, MO

Aeromatic Inc., Somerville, N.J.

Carle and Montanari Inc., Hackensack, NJ

I. Holland Ltd., Nottingham, U.K.

Auxiliary Equipment

There are some common auxiliary pieces of equipment that increase the efficiency of the tablet compression operation. In many cases, the speed of the die table is such that the dwell time of a die under the feed frame is too short to allow for adequate or consistent gravity filling of the die with granulation. Improper filling of the dies with granulation results in unsatisfactory weight variation and content uniformity of the resulting tablets. A similar result can occur with a poorly flowing granulation. To help alleviate these problems, mechanized feeders can be employed to force granulation into the dies (Fig. 11-10).

The high tablet output rates of modern presses demand that the granulation hoppers be refilled at frequent intervals; the larger the tablet is, the more frequently the hopper needs to be replenished. Allowing a tablet machine to run "dry" results in a series of rapidly degenerating and unacceptable events. First, low-weight tablets and tablets with poor weight variation are produced. Then, the soft granulation is unable to be formed into tablets. Finally, the tooling is usually ruined, particularly with thin tablets, by the punches being forced together without any granulation between them. Because of the relatively low volume of press hoppers, the filling of hoppers by hand on high-speed presses is inefficient, increases the risk of punch damage, and can contribute to weight variation problems. Therefore, mechanized equipment has been developed to load granulation into the press hoppers.

A popular method of handling large quantities of material is to place bulk granulation containers directly above tabletting machines to gravity-feed the granulation into hoppers. This can be accomplished by several means. Bulk granulation containers can be placed on floors above a tablet machine, and granulation can then be directed through openings in the floor into the hoppers. In a similar fashion, granulation containers can be held on mezzanines above tablet machines. If such overhead room is unavailable, hoists and mechanical lifts can be used to elevate granulation containers or material transfer devices directly in position above the press. Granulation level sensors can be used to stop the press automatically when the granulation level drops to a critical level in the hopper.

The high rate of tablet output with modern presses calls for a higher frequency or even continuous monitoring of tablet weight. Electronic monitoring devices, such as the Thomas Tablet Sentinel (Fig. 11-11), Pharmakontroll, and the Kilian Control System-MC, monitor the force at each compression station, which correlates with tablet weight. These monitors are also capable of initiating corrective actions, altering the amount

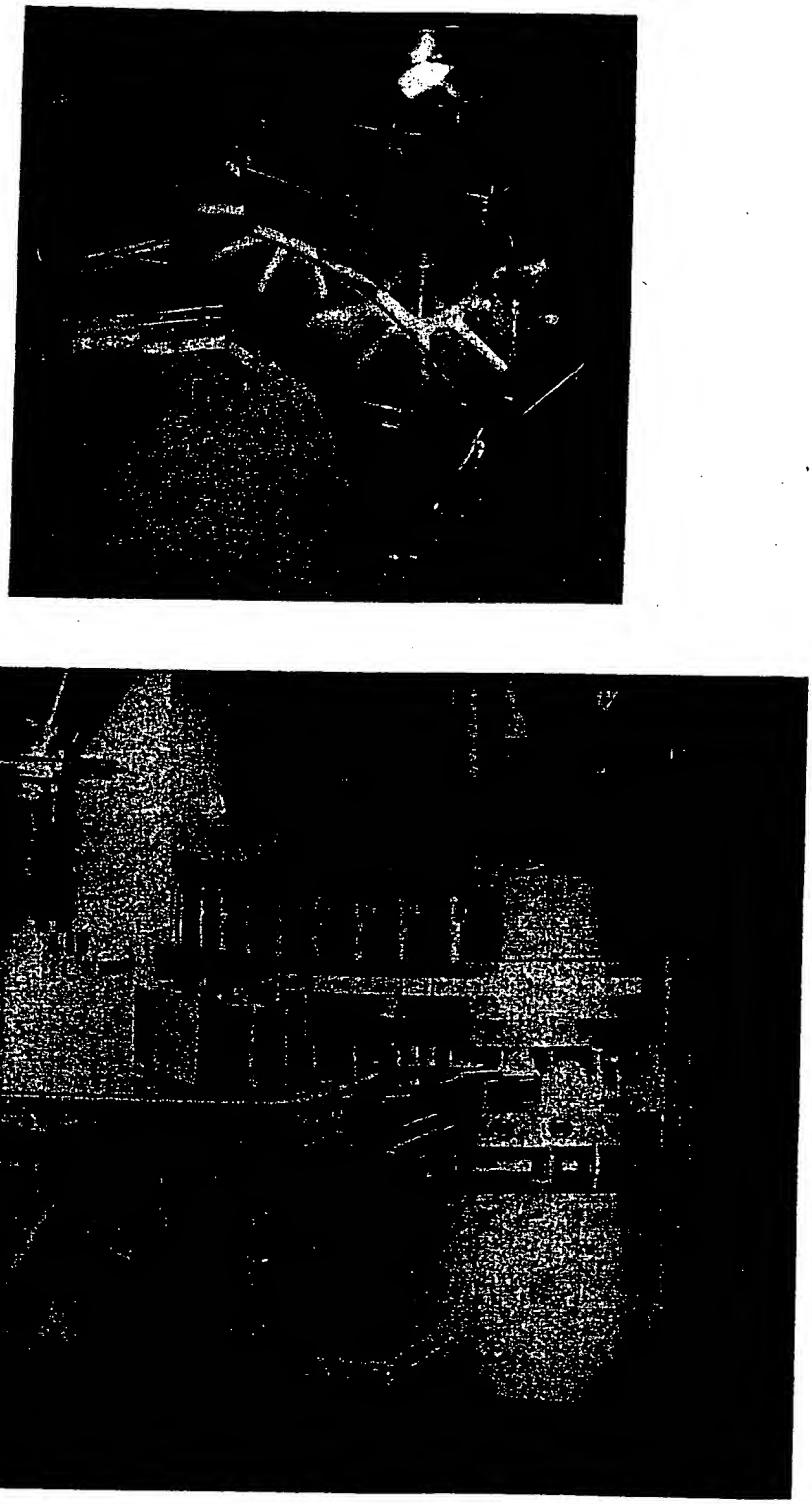

FIG. 11-10. A, *Manesty granulation feeding device. (1) Granulation input port from tablet machine feed hopper. (2) Rotating feed fingers. (3) Compressed tablet scrape-off blade.* B, *Manesty granulation feeding device mounted on a rotary tablet machine. (1) Tablet machine turret. (2) Tablet machine hopper. (3) Feeding device. (4) Compressed tablet output chute. (Courtesy of Thomas Engineering, Hoffman Estates, IL.)*

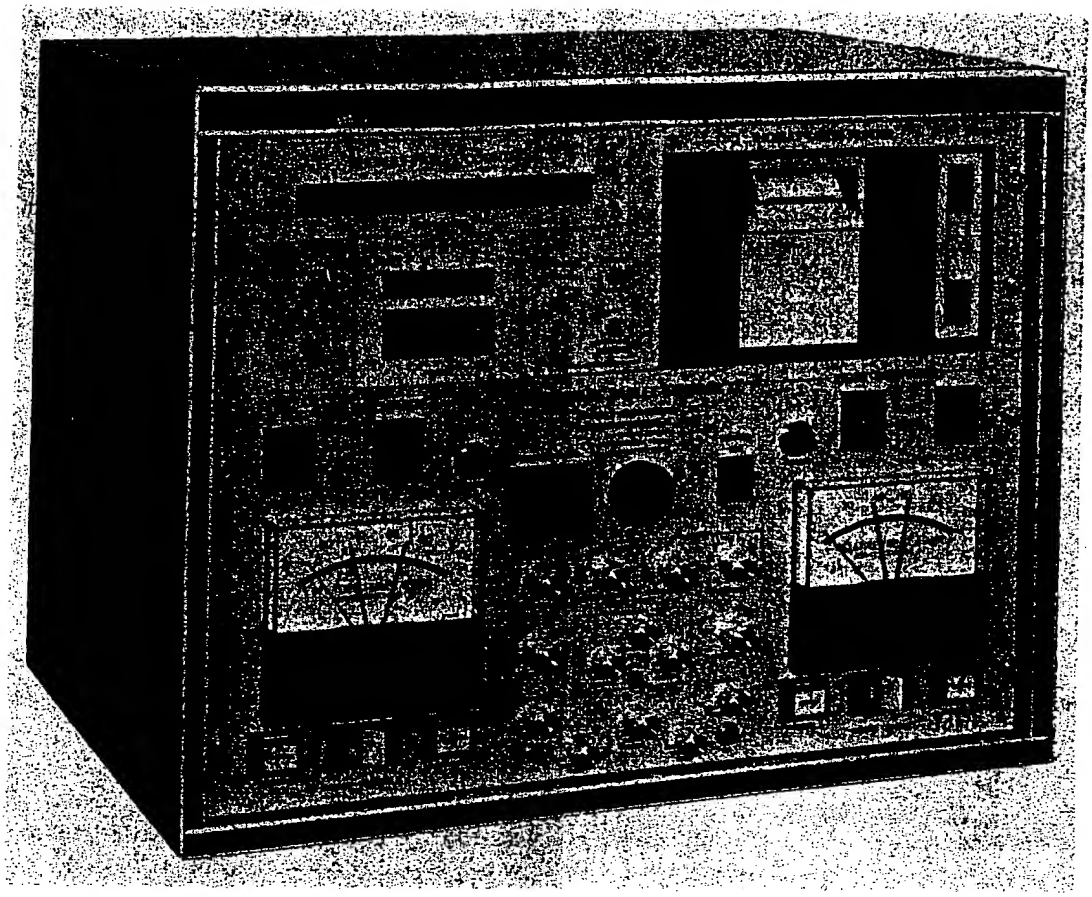

FIG. 11-11. *Thomas Table Sentinel II. (Courtesy of Thomas Engineering, Hoffman Estates, IL.)*

of die fill to maintain a fixed force, ejecting tablets that are out of specification, counting, and documenting the machine operation throughout the run.

In almost all cases, tablets coming off a tablet machine bear excess powder and are run through a tablet deduster to remove that excess.

In-Process Quality Control

During the compression of tablets, in-process tests are routinely run to monitor the process, including tests for tablet weight, weight variation, hardness, thickness, disintegration, and various evaulations of elegance. The in-process tests are performed by production and/or quality control (QC) personnel. In addition, many in-process tests are performed during product development by the formulator. Such testing during development has become increasingly important in recent years for process validation purposes. The data supplied by the formulator is usually employed by QC personnel to establish the test limits. At the start-up of a tablet compression operation, the identity of the granulation is verified, along with the set-up of the proper tabletting machine and proper tooling.

Processing Problems

In the normal process of developing formulations, and in the routine manufacture of tablets, various problems occur. Sometimes, the source of the problem is the formulation, the compression equipment, or a combination of the two.

Capping and Lamination. *Capping* is a term used to describe the partial or complete separation of the top or bottom *crowns* of a tablet from the main body of the tablet. *Lamination* is the separation of a tablet into two or more distinct layers. Usually, these processing problems are readily apparent immediately after compression; however, capping and lamination may occur hours or even days later. Subjecting tablets to the friability test described earlier is the quickest way of revealing such problems. Capping and lamination have in the past been attributed to air entrapment. During the compression process, air is entrapped among the particles or granules and does not escape until the compres-

sion pressure is released. Research has shown, however, that capping and lamination are due to the deformational properties of the formulation during and immediately following compression.[6,23]

During compaction, particles undergo sufficient plastic deformation to produce die-wall pressures greater than can be relieved by elastic recovery when the punch pressure is removed. In some materials, this die-wall pressure causes enough internal stress to cause a crack to propagate and initiate fracture of the compact in the die. If the excess stresses do not initiate fracture upon decompression in the die, the compact may laminate or cap upon ejection from the die. As the compact is ejected, the die-wall pressure falls to zero. The emerging portion of the compact expands while the confined portion cannot, thus concentrating shear stresses at the edge of the die and causing a break to develop. Tablets that do not fracture have the ability to relieve the shear stresses developed during decompression and/or ejection by plastic deformation. This stress relaxation is time-dependent; therefore, the occurrence of tablet fracture is also time-dependent. Intact tablets of acetaminophen, methenamine, and erythromycin can be made if the decompression is extended for several hours. Rapid decompression results in tablets that fracture. Stress relaxation could be the explanation for some practical tabletting problems. Tablet lamination or capping problems are often eliminated by precompression, slowing the tabletting rate, and reducing the final compression pressure. As the stress relaxation time is increased, the amount of stress needing to be relieved is reduced, allowing an intact compact to be formed.

Often, deep concave punches produce tablets that cap. The curved part of such tablets expands radially while the body of the tablet cannot, which establishes a shear stress that produces the fracture. Flat punches may eliminate this additional shear stress.

A certain percentage of moisture is often essential for good compaction. A granulation that is too dry tends to cap or laminate for lack of cohesion. For moisture-critical granulations, the addition of a hygroscopic substance, e.g., sorbitol, methylcellulose, or polyethylene glycol 4000, can help to maintain a proper moisture level. Capping and lamination may also be encountered in direct compression product development. Some powder or fine particulate materials may not be compressible or may have poor compression properties. Relative compressibility of various materials may be reflected by their degree of consolidation (crown thickness) when compressed in standard tooling under identical compression conditions.

Tablet tooling can also be a cause of capping. The concave or beveled edge faces of punches gradually curve inward with use and form a "claw" that can pull off the crowns of a tablet. Wear in the upper punch guides accelerates this claw formation by permitting the punch tips to strike the edges of the die holes. Also, the greater the radius of curvature of the punch face, the greater is the force exerted on the edges and the less on the center of the tablet at the moment of compression.

Dies develop a wear "ring" in the area of compression. As the ring develops, and enlarges, the tablets that are compressed in the rings have a diameter that is too large to pass easily through the narrower portion of the die above the ring. Upon ejection, this constriction causes the tablet to cap or laminate. A simple solution of this particular problem is to turn the die over so that compression occurs in an unworn area above the ring. On some presses, the depth of penetration of the upper punch can be regulated so that compression may be performed over some range of locations within the die. There are also dies available with tungsten carbide inserts. The carbide is so durable that the casing wears out before the insert does. Wear on tablet tooling increases as the hardness of the material being compressed increases. Most organic materials are soft; certain inorganic materials such as magnesium trisilicate are relatively hard and abrasive.

Another cause of capping is an incorrect setup at the press. When a compressed tablet is ejected from a die, the lower punch must rise flush with or protrude slightly above the face of the die at the point where the tablet strikes the sweep-off blade. If the punch remains below the face of the die, the sweep-off blade cuts off the tablet, leaving the bottom in the die. A less severe result of this incorrect adjustment is that the edge of the tablet catches on the die and chip. An incorrect adjustment of the sweep-off blade can also result in tablet fracture. If the blade is adjusted too high, tablets can start to travel under it, become stuck, and break off. The resulting broken pieces of tablets then enter the feed frame; if they are large enough, they can cause a disruption of the granulation feed, as well as affect the weight and hardness of subsequent tablets.

Picking and Sticking. "Picking" is a term used to describe the surface material from a tablet that is sticking to and being removed from the tablet's surface by a punch. Picking is of particular concern when punch tips have engraving

or embossing. Small enclosed areas such as those found in the letters "B," "A," and "O" are difficult to manufacture cleanly. Tablet materials that stick to the punches can accumulate to the point of obliterating the tip design. "Sticking" refers to tablet material adhering to the die wall. When sticking occurs, additional force is required to overcome the friction between the tablet and the die wall during ejection. Serious sticking at ejection can cause chipping of a tablet's edges and can produce a rough edge. Also, a sticking problem does not allow the lower punches free movement and therefore can place unusual stresses on the cam tracks and punch heads, resulting in their damage. Sticking can also apply to the buildup of material on punch faces.

These flaws have many remedies. Lettering should be designed as large as possible, particularly on punches with small diameters. The tablet can perhaps be reformulated to a larger size. Plating of the punch faces with chromium is a method for producing a smooth, nonadherent face.

In some cases, colloidal silica added to the formula acts as a polishing agent and makes the punch faces smooth so that material does not cling to them. On the other hand, the frictional nature of this material may require additional lubrication to facilitate release of the tablet from the die. Sometimes, additional binder or a change in binder may make the granules more cohesive, and therefore less adherent, than before.

Low-melting-point substances, either active ingredients or additives such as stearic acid and polyethylene glycol, may soften sufficiently from the heat of compression to cause sticking. Dilution of the active ingredient with additional higher-melting-point materials and a consequent increase in the size of the tablet may help. The level of low-melting-point lubricants may be reduced, or higher-melting-point replacements may be substituted. When a low-melting-point medicament is present in high concentration, refrigeration of the granulation and the press may be in order. Excessive moisture may be responsible for sticking, and further drying of the granulation is then required.

Mottling. Mottling is an unequal distribution of color on a tablet, with light or dark areas standing out in an otherwise uniform surface. One cause of mottling is a drug whose color differs from the tablet excipients or a drug whose degradation products are colored. The use of colorants may solve the above problem but can create others. A dye can cause mottling by migrating to the surface of a granulation during drying. To overcome this difficulty, the formulator may change the solvent system, change the binder system, reduce the drying temperature, or grind to a smaller particle size. The use of colorants in direct compression formulations can lead to mottling if the dye is not well dispersed or if its particle size is too large.

Certain colored adhesive gel solutions may not be distributed well because they must be hot when added to much cooler powder mixtures. The adhesive then precipitates from solution and carries most of the color with it. Further wetting, even overwetting, is needed to disperse the binder and the color. The additional mixing and increased activation of the binder, however, may result in tablets with increased disintegration times. Therefore, a better practice may be to incorporate fine powder adhesives such as acacia and tragacanth into the product before adding the granulating fluid, or to disperse a dry color additive during the powder blending step.

Weight Variation. In previous sections, weight variation of tablets has been mentioned as an important in-process control measurement, and weight variation specifications have been given. The weight of a tablet being compressed is determined by the amount of granulation in the die prior to compression. Therefore, anything that can alter the die-filling process can alter tablet weight and weight variation.

Granule Size and Size Distribution Before Compression. Variations in the ratio of small to large granules and in the magnitude of difference between granule sizes influence how the void spaces between particles are filled. Thus, although the apparent volume in the die is essentially the same, different proportions of large and small particles may change the weight of fill in each die. Furthermore, if large granules are being used to fill a small die cavity, relatively few granules are required, and the difference of only a few granules around the average may represent a high percentage weight variation. If hundreds of granules are required on the average for die fill, a variation of a few granules around the average would produce a minor weight variation, given a narrow particle size range.

Poor Flow. The die-fill process is based on a continuous and uniform flow of granulation from the hopper through the feed frame. When the granulation does not flow readily, it tends to move spasmodically through the feed frame so that some dies are incompletely filled. Similarly, dies are not filled properly when machine speed is in excess of the granulation's flow capabilities. With poor flow, the addition of a glidant such as talcum or colloidal silica, or an increase in the amount already present, may be helpful.

Also available are induced die feeders, which mechanically "force" the granulation down into the die cavities as they pass beneath the feed frame.

Poor flow through the feed frame is usually a sign that the granulation is not flowing properly out of the hopper. As particulate solids move under the force of gravity through progressively smaller openings, they are subjected to uneven pressures from the mass above and alongside. Depending on the geometry of the hopper, this situation may give rise to one or another of two causes for poor flow: "arching" or "bridging," and "rat-holing." Figure 11-12 illustrates these phenomena. When poor hopper flow occurs, it may be controllable with vibrators attached to the hopper sides to induce the granulation flow.

Devices designed to improve poor flow characteristics of materials often introduce another problem, however. Since most tablet granulations consist of materials with a range of particle sizes, the vibration or mixing action of the flow-promoting devices may induce segregation and stratification of the particles. The larger particles tend to drift upward while the smaller particles sift downward. Not only can the resulting "classification" of particle sizes cause appreciable changes in tablet weight and weight variation as described earlier, but it can also lead to poor content uniformity, since drug is often not uniformly distributed between the larger and smaller particles. Poor particulate flow may be caused not by the granulation, but by poor design of the granulation hopper, which can be exaggerated by dents that effectively cut off the flow. Poor weight variation can also be caused by surges of excessive flow. Direct compression granulations fed through typical wet-granulation hoppers and feed frames are prone to this type of flow. Often, restricting the flow out of the hopper corrects the problem. Recently, a patent was issued for a new feed frame design that accommodated excessive flow from the hopper without compromising uniform weight variation.[24]

Poor Mixing. Sometimes, the lubricants and glidants are not thoroughly distributed. The flow of particles is then impaired, and the granules do not move efficiently into the dies. There is a tendency to minimize the mixing time during lubricant addition to prevent or reduce granule friability; however, inadequate mixing at this stage can result in unsatisfactory granulation flow.

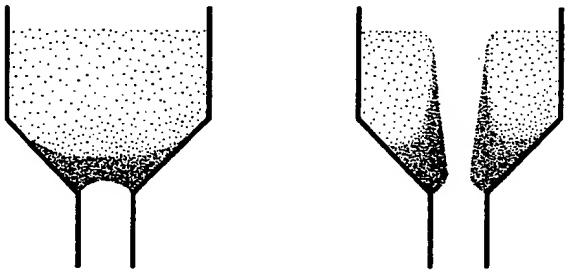

FIG. 11-12. *Bridging (left); rat-holing (right).*

Punch Variation. When lower punches are of unequal lengths—the difference may be only a few thousandths of an inch—the fill in each die varies because the fill is volumetric. Only a good punch and die control program can provide tooling of uniform dimensions.

Hardness Variation. Hardness variation is a problem that has the same causes as weight variation. Hardness depends on the weight of material and the space between the upper and lower punches at the moment of compression. If the volume of material or the distance between punches varies, hardness is likewise inconsistent.

Double Impression. A last problem for discussion is that of double impression. This involves only punches that have a monogram or other engraving on them. At the moment of compression, the tablet receives the imprint of the punch. On some machines, the lower punch is free to drop and then travel uncontrolled for a short distance before it rides up the ejection cam to push the tablet out of the die. During its free travel, it rotates. At this point, the punch may make a new, although lighter, impression on the bottom of the tablet, resulting in a double imprint. Similar problems can be encountered with engraved upper punches and tablet machines that utilize two compression stages to compress a tablet. The first stage, *precompression,* uses a lower compaction force than the final compression stage, but the tablet does receive the imprint of the punch. If the upper punch is uncontrolled, it can rotate during the short travel to the final compression stage and thus create a double imprint. The newer presses have antiturning devices as an integral part of their design and construction.

Tablet Granulations

Basic Characteristics

The characteristics of a tablet that make it a popular dosage form, e.g., compactness, physical stability, rapid production capability, chemical stability, and efficacy, are in general dictated primarily by the qualities of the granulation from which it is made. Basically stated, materials intended for compaction into a tablet must

possess two characteristics: fluidity and compressibility. To a great extent, these properties are required by the compression machine design. As previously discussed, good flow properties are essential for the transport of the material through the hopper, into and through the feed frame, and into the dies. Tablet materials should therefore be in a physical form that flows smoothly and uniformly. The ideal physical form for this purpose is spheres, since these offer minimum contact surfaces between themselves and with the walls of the machine parts. Unfortunately, most materials do not easily form spheres; however, shapes that approach spheres improve flowability. Therefore granulation is in part the pharmaceutical process that attempts to improve the flow of powdered materials by forming spherelike or regularly shaped aggregates called *granules*. The need to assess the shape of particles and their relative regularity or approximation to spheres has led to the development of equations whereby certain "factors" can be calculated to provide quantitative comparisons of different particle shapes. By measuring particle surface area (S), volume (V) and a projected equivalent diameter (d_p), a volume shape factor (α_v), a surface shape factor (α_s), and a shape coefficient (α_{vs}) can be calculated using equations (1) to (3) for quantitative work.[25]

$$\alpha_s = \frac{S}{d_p^2} \quad (1)$$

$$\alpha_v = \frac{V}{d_p^2} \quad (2)$$

$$\alpha_{vs} = \frac{\alpha_s}{\alpha_v} \quad (3)$$

The shape coefficient for a sphere is 6. As a particle becomes more irregular in shape, the value of α_{vs} increases. For a cube, α_{vs} is equal to 6.8.

The other desirable characteristic, compressibility, is the property of forming a stable, compact mass when pressure is applied. The requisite physical properties and the forces that hold the tablet together are discussed in Chapter 4, "Compression and Consolidation of Powdered Solids." The consideration of compressibility in this discussion is limited to stating that granulation is also the pharmaceutical process that converts a mixture of powders, which have poor cohesion, into aggregates capable of compaction.

Granulation Properties

There are many formulation and process variables involved in the granulation step, and all of these can affect the characteristics of the granulations produced. Therefore, methods to measure certain granulation characteristics have been developed to monitor granulation suitability for tabletting.

Particle Size and Shape. The particle size of a granulation is known to affect the average tablet weight, tablet weight variation, disintegration time, granule friability, granulation flowability, and the drying rate kinetics of wet granulations.[26–28] The exact effect of granule size and size distribution on processing requirements, bulk granulation characteristics, and final tablet characteristics depends upon the formulation ingredients and their concentrations, as well as the type of granulating equipment and processing conditions employed. Therefore, the formulator should determine for each formulation and manufacturing process the effects of granule size and size distribution on processability and tablet quality features. The methods for measuring and interpreting particle size and particle size distribution are discussed in Chapter 2, "Milling."

Surface Area. The determination of the surface area of finely milled drug powders may be of value for drugs that have only limited water solubility. In these cases, particle size, and especially the surface area of the drug, can have a significant effect upon dissolution rate. The determination of the surface area of granulations is not a common practice. In general, if one is interested in effects of granulation surface upon measurable properties of the final dosage form, particle size of the granulation is measured. An inverse relationship normally exists between particle size and surface area; however, granulations can have convoluted structures with considerable internal surface. Technology available for determining the surface area of coarse powders or agglomerates (granulations) is not as advanced as that available for fine powders. The two most common methods for determining surface area of solid particles are gas adsorption and air permeability. In the first method (gas adsorption), the amount of gas that is adsorbed onto the powder to form a monolayer is measured and then used to calculate the surface area of the powder sample. Air permeability, the rate at which air permeates a bed of powder, is used to calculate the surface area of the powder sample. These methods are described in Chapter 4.

Density. Granule density may influence compressibility, tablet porosity, dissolution, and other properties. Dense, hard granules may require higher compressible loads to produce a cohesive compact, let alone tablets of acceptable appearance that are free from visible granule

boundaries. The higher compression load, in turn, has the potential of increasing the tablet disintegration and drug dissolution times. Even if the tablets disintegrate readily, the harder, denser granules may dissolve less readily. At the same time, harder, denser granules are usually less friable. Basically, two methods are used to determine granule density. Both involve the use of a pycnometer. In one, the intrusion fluid is mercury, and in the other, it is a solvent of low surface tension (e.g., benzene) in which the granules are not soluble. The accuracy of these pycnometer methods depends on the ability of the intrusion fluids to penetrate the pores of the granules. Density is calculated from the volume of intrusion fluid displaced in the pycnometer by a given mass of granulation:[25]

$$D = M/V_p - V_i \quad (4)$$

where D is density, V_p is the total volume of the pycnometer, and V_i is the volume of intrusion fluid containing that mass of granules (M) that is required to fill the pycnometer.

The term *bulk density* refers to a measure used to describe a packing of particles or granules. The equation for determining bulk density (ρ_b) is:[25]

$$\rho_b = \frac{M}{V_b} \quad (5)$$

where M is the mass of the particles and V_b is the total volume of packing. The volume of the packing can be determined in an apparatus consisting of a graduated cylinder mounted on a mechanical tapping device that has a specially cut rotating cam. An accurately weighed sample of powder or granulation is carefully added to the cylinder with the aid of a funnel. Typically, the initial volume is noted, and the sample is then tapped until no further reduction in volume is noted. The volume at this tightest packing is then used in equation (1) to compute bulk density ρ_b. A sufficient number of taps should be employed to assure reproducibility for the material in question. The tapping should not produce particle attrition or a change in the particle size distribution of the material undergoing testing. See Chapter 4 for further details.

An important measure that can then be obtained from bulk density determinations is the percent compressibility, C, which is defined as follows:[25]

$$C = \frac{\rho_b - \rho_u}{\rho_b}(100) \quad (6)$$

where ρ_u is the untapped bulk density (often called *loose* or *aerated* bulk density). In theory, the more compressible a bed of particulates is, the less flowable the powder or granulation will be. Conversely, the less compressible a material is, the more flowable it will be.

Bulk density largely depends on particle shape. As the particles became more spherical in shape, bulk density is increased. In addition, as granule size increases, bulk density decreases. The smaller granules are able to form a close, more intimate packing than larger granules.

Strength and Friability. A granule is an aggregation of component particles that is held together by bonds of finite strength. The strength of a wet granule is due mainly to the surface tension of liquid and capillary forces. These forces are responsible for initial agglomeration of the wet powder. Upon drying, the granule has strong bonds resulting from fusion or recrystallization of particles and curing of the adhesive or binder. Under these conditions, van der Waals forces are of sufficient strength to produce a strong, dry granule. Measurements of granule strength are therefore aimed at estimating the relative magnitude of attractive forces seeking to hold the granule together. The resultant strength of a granule depends, of course, on base material, the kind and amount of granulating agent used, the granulating equipment used, and so forth. Factors affecting granule strength are discussed in this section.

Granule strength and friability are important, as they affect changes in particle size distribution of granulations, and consequently, compressibility into cohesive tablets. When determining a relative measure of granule strength, two distinct types of measurements can be made. Perhaps, the one most commonly used is that of compression strength. In this test, a granule is placed between anvils, and the force required to break the granule is measured.[29,30] Other common methods of studying granule strength are those that relate to friability measurements. Most of these methods are variations of the American Society for Testing Materials (ASTM) tumbler test for the friability of coal, and provide a means of measuring the propensity of granules to break into smaller pieces when subjected to disruptive forces.[31]

Flow Properties. The flow properties of a material result from many forces. Solid particles attract one another, and forces acting between particles when they are in contact are predominately surface forces. There are many types of forces that can act between solid particles: (1) frictional forces, (2) surface tension forces, (3) mechanical forces caused by interlocking of

particles of irregular shape, (4) electrostatic forces, and (5) cohesive or van der Waals forces. All of these forces can affect flow properties of a solid. They can also affect granule properties such as particle size, particle size distribution, particle shape, surface texture or roughness, residual surface energy, and surface area. With fine powders ($\leq 150\mu m$), the magnitude of the frictional and van der Waals forces usually predominate. For larger particles ($\geq 150\mu m$) such as granules produced by a wet granulation technique, frictional forces normally predominate over van der Waals forces. Also, as particles increase in size, mechanical or physical properties of particles and their packings become important. While an evaluation of some of the fundamental properties of particles discussed earlier (e.g., shape and bulk density) is important, there are tests that can be employed as flow measurements of the effect of all the interparticulate forces acting at once. Two of the most common methods are (1) repose angle, and (2) hopper flow rate measurements.

Repose Angle. The fixed funnel and free-standing cone methods employ a funnel that is secured with its tip at a given height, H, above graph paper that is placed on a flat horizontal surface. Powder or granulation is carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. Thus, with R being the radius of the base of the conical pile:

$$\tan \alpha = \frac{H}{R} \qquad (7)$$

or

$$\alpha = \arctan \frac{H}{R} \qquad (8)$$

where α is the angle of repose. The fixed cone method establishes the diameter of the cone base by using a circular dish with sharp edges. Powder is poured onto the center of the dish from a funnel that can be raised vertically until a maximum cone height, H, is obtained. The repose angle is calculated as before. In the tilting box method, a rectangular box is filled with powder and tipped until the contents begin to slide. In the revolving cylinder method, a cylinder with a transparent end is made to revolve horizontally when half filled with powder. The maximum angle that the plane of powder makes with the horizontal surface on rotation is taken as the angle of repose. The angle determined by these first three methods is often referred to as the *static angle of repose,* and the angle arrived at in the last method is commonly called the *kinetic* or *dynamic angle of repose.* Values for angles of repose $\leq 30°$ usually indicate a free-flowing material and angles $\geq 40°$ suggest a poorly flowing material. As mentioned previously, flow of coarse particles is also related to packing densities and mechanical arrangements of particles. For this reason, a good auxiliary test to run in conjunction with the repose angle test is the compressibility test, discussed previously. From the angle of repose and compressibility values, a reasonable indication of a material's inherent flow properties should be possible.

Hopper Flow Rates. Hopper flow rates have been used as a method of assessing flowability. Instrumentation to obtain hopper flow rates continually monitors the flow of material out of conical hoppers onto a recording balance device. Instrumentation of this kind is quite simple, and results are easy to interpret, making the method attractive from a pragmatic standpoint. Unfortunately, the two methods used for studying flow, hopper tests and repose angles, do not correlate well.

Compaction. The process of consolidating and compacting powder or granule materials to form a tablet is complex, owing to the numerous internal events that act simultaneously (see Chap. 4). The basic tool that has been developed for studying the compression process is the instrumented tablet press. Tablet presses are instrumented by affixing transducers to measure the forces applied during the compression process. The signals produced by the transducer system are then monitored by some means—most recently, by computer. Properly instrumented and monitored tablet presses have been shown to be of great assistance in studying the mechanism of compaction, the relationship of compaction mechanism to tablet properties, and various formulation evaluations. Such studies have also allowed for the development of compression profile references for comparison, the development of automatic control systems, and the monitoring of tooling wear.[32]

Manufacture of Granulations

Dry Manufacturing Methods

The manufacture of granulations for tablet compression may follow one or a combination of three established methods: the dry methods of direct compression, compression granulation, and wet granulation. Table 11-3 compares the type and number of processing steps commonly

required with each technique. A consideration of the important aspects of these processes illustrates the advantages and disadvantages of each.

Direct C mpression. There are a few crystalline substances, such as sodium chloride, sodium bromide, and potassium chloride, that may be compressed directly. The vast majority of medicinal agents are rarely so easy to tablet, however. In addition, the compression of a single substance may produce tablets that do not disintegrate. If disintegration is a problem, other components are needed, which in turn may interfere with the compressibility of the active ingredient and thus minimize the usefulness of the method. Most materials possess relatively weak intermolecular attraction or are covered with films of adsorbed gases that tend to hinder compaction. Thus, most large-dose drugs do not lend themselves to this process. With many other drugs having small doses, uniform blends of the drug and coarser direct compression diluents cannot be achieved, which makes this process impractical. However, the use of compressible diluents with many moderate-dose drugs makes this process the most streamlined method of tablet manufacture (Table 11-3).

A directly compressible diluent is an inert substance that may be compacted with little difficulty and may compress even when quantities of drugs are mixed with it. Compression capacity is still maintained when other tablet materials necessary for flow, disintegration, and so forth are blended in. Directly compressible vehicles are examined in detail later in this chapter. Direct compression materials, in addition to possessing good flow and compressibility, must be inert, tasteless, reworkable, able to disintegrate, and inexpensive.

Even though direct compression has some important advantages (low labor input, a dry process, fewest processing steps) there are some limitations to the technique.

1. Differences in particle size and bulk density between the drug and diluent may lead to stratification within the granulation. The stratification may then result in poor content uniformity of the drug in the compressed tablet. The stratification and resultant content uniformity problems are of special concern with low-dose drugs.
2. A large-dose drug may present problems with direct compression if it is not easily compressible by itself. To facilitate compression, noncompressible large-dose drugs, which are usually restricted to about 30% of a direct compression formula, could require an amount of diluent so large that the resultant tablet is costly and difficult to swallow.
3. In some instances, the direct compression diluent may interact with the drug. A good example of such a reaction is that which occurs between amine compounds and spray-dried lactose, as evidenced by a yellow discoloration.
4. Because of the dry nature of direct compression, static charge buildup can occur on the drug during routine screening and mixing, which may prevent a uniform distribution of the drug in the granulation.

The equipment and procedures used in direct compression are basically screening or milling and mixing. These topics are covered in Chapter 1, "Mixing," and Chapter 2, "Milling."

Compression Granulation. Compression granulation has been used for many years, and is a valuable technique in situations where the effective dose of a drug is too high for direct compaction, and the drug is sensitive to heat, moisture, or both, which precludes wet granulation. Many aspirin and vitamin formulations are prepared for tabletting by compression granulation.

Compression granulation involves the compaction of the components of a tablet formulation by means of a tablet press or specially designed machinery, followed by milling and screening, prior to final compression into a tablet. When the initial blend of powders is forced into the dies of a large-capacity tablet press and is compacted by means of flat-faced punches, the compacted masses are called *slugs*, and the process is referred to as "slugging." The slugs are then screened or milled to produce a granular form of tabletting material, which now flows more uniformly than the original powder mixture. When a single slugging process is insufficient to confer the desired granular properties to the material, the slugs are sometimes screened, slugged again, and screened once more.

TABLE 11-3. *Processing Steps Commonly Required in the Various Tablet Granulation Preparation Techniques*

Processing Step	*Wet*	*Dry*	*Direct*
Raw material	X	X	X
Weigh	X	X	X
Screen	X	X	X
Mix	X	X	
Compress (slug)		X	
Wet mass	X		
Mill	X		
Dry	X		
Mill	X	X	
Mix	X	X	
Compress	X	X	X

Slugging is just an elaborate method of subjecting a material to increased compression time. The act of slugging followed by screening and subsequent compression of the particles is roughly equivalent to an extended dwell time during compression in a tablet machine. The two or more times that the material is subjected to compaction pressures causes a strengthening of the bonds that hold the tablet together. The resultant granules also increase the fluidity of these powder mixtures, which by themselves do not flow well enough to fill the dies satisfactorily.

As shown in Table 11-3, the compression granulation method requires less equipment and space than other methods, and eliminates the addition of moisture and the application of heat, as found in the wet massing and drying steps of the wet granulation method.

On a large scale, compression granulation can also be performed on a specially designed machine called a *roller compactor*. Roller compactors are capable of producing as much as 500 kg per hour or more of compacted ribbon-like material, which can then be screened or milled into a granulation suitable for compression into tablets.

Roller compactors, utilize two rollers that revolve toward each other (Fig. 11-13). By means of a hydraulic ram forcing one of the rollers against the other, the machine is capable of exerting known fixed pressures on any powdered material that flows between the rollers. Powdered material is fed between the rollers by a screw conveyor system. After passing through the rollers, the compacted mass resembles a thin wide ribbon that has fallen apart into large segments. These are equivalent to the slugs produced by the slugging process. The segments are then screened or milled for the production of granules.

The compaction force of the roller compactor is controlled by three variables: (1) the hydraulic pressure exerted on the compaction rolls, (2) the rotational speed of the compaction rolls, and (3) the rotational speed of the feed screws. The roll speed and the feed-screw speed have the greatest effect on the compaction process. The feed screws on most modern compactors consist of a variable-speed horizontal and vertical screw. The horizontal screw picks up the powder from the hopper and maintains a continuous flow to the vertical screw. The vertical screw delivers the powder to the compaction rolls. The vertical screw speed is critical for uniform compaction. It serves to deaerate the powder and maintains a constant flow onto the compaction rolls. Any variation in deaeration or load causes extreme

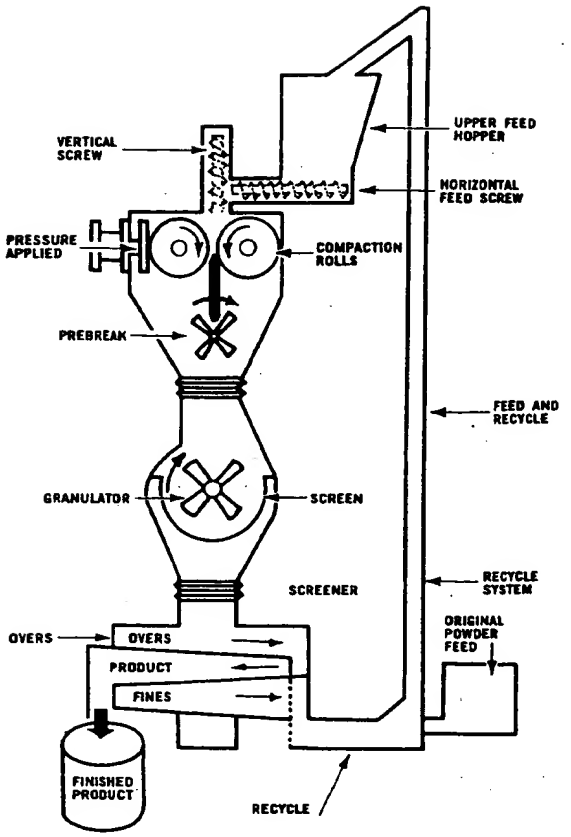

FIG. 11-13. *Schematic diagram of a Chilsonator roller compactor in a granulation production system. (Courtesy of the Fitzpatrick Company, Elmhurst, IL.)*

changes in the compact. The vertical feed screw is usually set so that it delivers more material than the compaction rolls accept, assuring constant loading during the compaction process. The speed of the compaction rolls controls the pressure dwell time, which has a great effect on the density and hardness of the compact.

A standard procedure for testing compaction uniformity and machine capacity is to select a hydraulic pressure in the mid-ranges of the equipment. Set the compaction roll at the slowest speed, and set the feed screw at the highest speed. If the powders are compactible in the first pass, the machine will overload. When this happens, the compaction roll speed should be increased until the loading is constant. Maximum throughput is achieved at this setting for the material being tested. If no overloading occurs, the powder should be passed through a second time, using the same procedure. The roller compactor offers the advantages over the slugging process of increased production capacity, greater control of compaction pressure and dwell time, and no need for excessive lubrication of the powder.

There are many modifications available on roll compactors. Roll designs cover a complete range from smooth to sign curves and serrated surfaces. The shapes and sizes of the screw feed assembly are available in a wide range of designs. Most compactors can be fitted with liquid-cooled rolls and chambers. All manufacturers of roller compactors have pilot plant facilities and offer complete testing programs. Trial runs are advisable, so that the compactor is suitable for the materials to be compacted.

Wet Granulation

The wet granulation technique uses the same preparatory and finishing steps (screening or milling, and mixing) as the two previously discussed granulation techniques. The unique portions of wet granulation process involve the wet massing of the powders, wet sizing or milling, and drying. The theory, equipment, and methods associated with drying are discussed in Chapter 3.

Methods. Wet granulation forms the granules by binding the powders together with an adhesive, instead of by compaction. The wet granulation technique employs a solution, suspension, or slurry containing a binder, which is usually added to the powder mixture; however, the binder may be incorporated dry into the powder mix, and the liquid may be added by itself.

The method of introducing the binder depends on its solubility and on the components of the mixture. Since, in general, the mass should merely be moist rather than wet or pasty, there is a limit to the amount of solvent that may be employed. Therefore, when only a small quantity is permissible, the binder is blended in with the dry powders initially; when a large quantity is required, the binder is usually dissolved in the liquid. The solubility of the binder also has an influence on the choice of methods, since the solution should be fluid enough to disperse readily in the mass.

The liquid plays a key role in the granulation process. Liquid bridges are developed between particles, and the tensile strength of these bonds increases as the amount of liquid added is increased. These surface tension forces and capillary pressure are primarily responsible for initial granule formation and strength. Once the granulating liquid has been added, mixing continues until a uniform dispersion is attained and all the binder has been activated. During granulation, particles and agglomerates are subjected to consolidating forces by action of machine parts and of interparticulate forces. Granulation in large blenders requires 15 min to an hour. The length of time depends on the wetting properties of the powder mixture and the granulating fluid, and upon the efficiency of the mixer. A rough way of determining the end point is to press a portion of the mass in the palm of the hand; if the ball crumbles under moderate pressure, the mixture is ready for the next stage in processing, which is wet screening.

The wet screening process involves converting the moist mass into coarse, granular aggregates by passage through a hammer mill or oscillating granulator, equipped with screens having large perforations. The purpose is to further consolidate granules, increase particle contact points, and increase surface area to facilitate drying. Overly wet material dries slowly and forms hard aggregates, which tend to turn to powder during subsequent dry milling. There are many instances in which wet milling may be omitted, with a considerable saving of time. The formulator should be alert to these opportunities and not follow the old method blindly.

A drying process is required in all wet granulation procedures to remove the solvent that was used in forming the aggregates and to reduce the moisture content to an optimum level of concentration within the granules. During drying, interparticulate bonds result from fusion or recrystallization and curing of the binding agent, with van der Waals forces playing a significant role.

After drying, the granulation is screened again. The size of the screen depends upon the grinding equipment used and the size of the tablet to be made.

The use of volatile or inflammable solvents for wet granulation creates other problems. Safety considerations demand that at a minimum, the work areas be well-ventilated to reduce direct toxic effects or to keep the solvent vapor concentration below explosion limits. Also, all equipment should be electrically grounded to prevent sparks that could initiate explosions. Explosion-proof or explosion-resistant motors may also be required. If solvent granulating systems are to be used, the entire process should be thoroughly discussed, and the facilities should be inspected by the company's safety engineer.

Exhausting solvent vapors or drying granulations made with solvents also requires special precautions. Environmental Protection Agency (EPA) regulations limit the amount of solvent vapors that can be exhausted into the atmosphere. Such EPA limits could require recovery or burning of the solvent vapors, which are expensive operations. Ovens employed for drying granulations wetted with explosive solvents should employ high airflow rates, to stay well

below vapor explosive limit concentrations in air. Such ovens should also contain appropriate controls to prevent explosions due to accumulation of vapors following a power outage or during later resumption of power.

Equipment. When traditional equipment is used in the conventional wet granulation scheme (Table 11-4), the entire process is labor-intensive and time-consuming. The equipment used for granulation is not highly effective for dry mixing. Therefore, in many instances, a different mixer is used for dry mixing prior to granulating. Examples are sigma blade and planetary mixers. Granulating mixers are slow, are generally poor powder mixers, and require care for even addition of granulating liquids. Also, considerable time is needed to distribute the binder properly throughout the mass.

While some tablets are still made in the traditional manner, newer equipment has been developed that can accomplish both dry mixing and wet granulation efficiently and in much less time. These new mixers are classified as high-speed mixer/granulators.

TABLE 11-4. *Some Common Tablet Excipients*

Diluents	
Lactose USP	Mannitol USP
Lactose USP, anhydrous	Sorbitol
Lactose USP, spray-dried	Sucrose USP powder
Directly compressible starches	Sucrose-based materials
Hydrolyzed starches	Calcium sulfate dihydrate NF
Microcrystalline cellulose NF	Dextrose
Other cellulose derivatives	
Dibasic calcium phosphate dihydrate NF	
Binders and Adhesives	
Acacia	Starch, pregelatinized
Cellulose derivatives	Sodium alginate and alginate derivatives
Gelatin	Sorbitol
Glucose	Tragacanth
Polyvinylpyrrolidone (PVP)	
Starch, paste	
Disintegrants	
Starch	Cellulose derivatives
Starch derivatives	Alginates
Clays	PVP, cross-linked
Cellulose	
Lubricants	
Stearic acid	Polyethylene glycols
Stearic acid salts	Surfactants
Stearic acid derivatives	Waxes
Talc	
Glidants and Flow Promoters	
Silica derivatives	
Talc	
Cornstarch	
Colors, Flavors and Sweeteners	
FD & C and D & C dyes and lakes	
Spray-dried and other flavors	
Natural sweeteners	
Artificial sweeteners	

The Littleford Lodige mixer was one of the first high-shear powder blenders capable of rapidly blending pharmaceutical powders and wet massing within the same equipment. With some formulations, the equipment may also be capable of producing agglomerated granular particles that are ready for fluid bed or other drying methods without further processing. Figure 11-14 illustrates a conventional Lodige mixer and describes the various assemblies of the unit. The unit consists of a horizontal cylindric shell equipped with a series of plow-shaped mixing tools and one or more high-speed blending chopper assemblies mounted at the rear of the mixer. When the chopper blades are operated during dry mixing, dry lumps of powder are effectively dispersed so that sieving is no longer an essential prerequisite of powder blending when this type of equipment is employed. For the addition of liquids, an injection tube terminating in one or more spray nozzles is provided. The nozzles are located immediately above the chopper assembly.

In operation, the plow-shaped mixing tools may be revolved at variable speeds to maintain the contents of the mixer in an essentially fluidized condition and provide a high-volume rate of transfer of material back and forth across the blender. When liquid granulating agents are added to dry powders, the liquid enters the mixer under pressure through the liquid nozzle immediately above the chopper assembly, or assemblies, and is immediately dispersed.

Using this type of high-shear powder mixing equipment, complete mixing may be obtained in as little as 30 to 60 sec. A temperature rise of 10 to 15° may be expected if dry blending is continued over a period of 5 to 10 min. When a high-speed, high-shear mixer of the Litteford Lodige type is used for wet granulation, the power used by the mixer increases as the powder mass becomes increasingly wet. Power usage is often reflected in the readings of an ammeter or wattmeter mounted on the equipment and may be useful in helping to identify the proper end point for the wet granulation process.

The Diosna mixer/granulator is another type of high-speed powder mixer and processor (Fig. 11-15). The mixer utilizes a bowl (1) mounted in the vertical position. A high-speed mixer blade (2) revolves around the bottom of the bowl. The blade fits over a pin bar at the bottom of the mix-

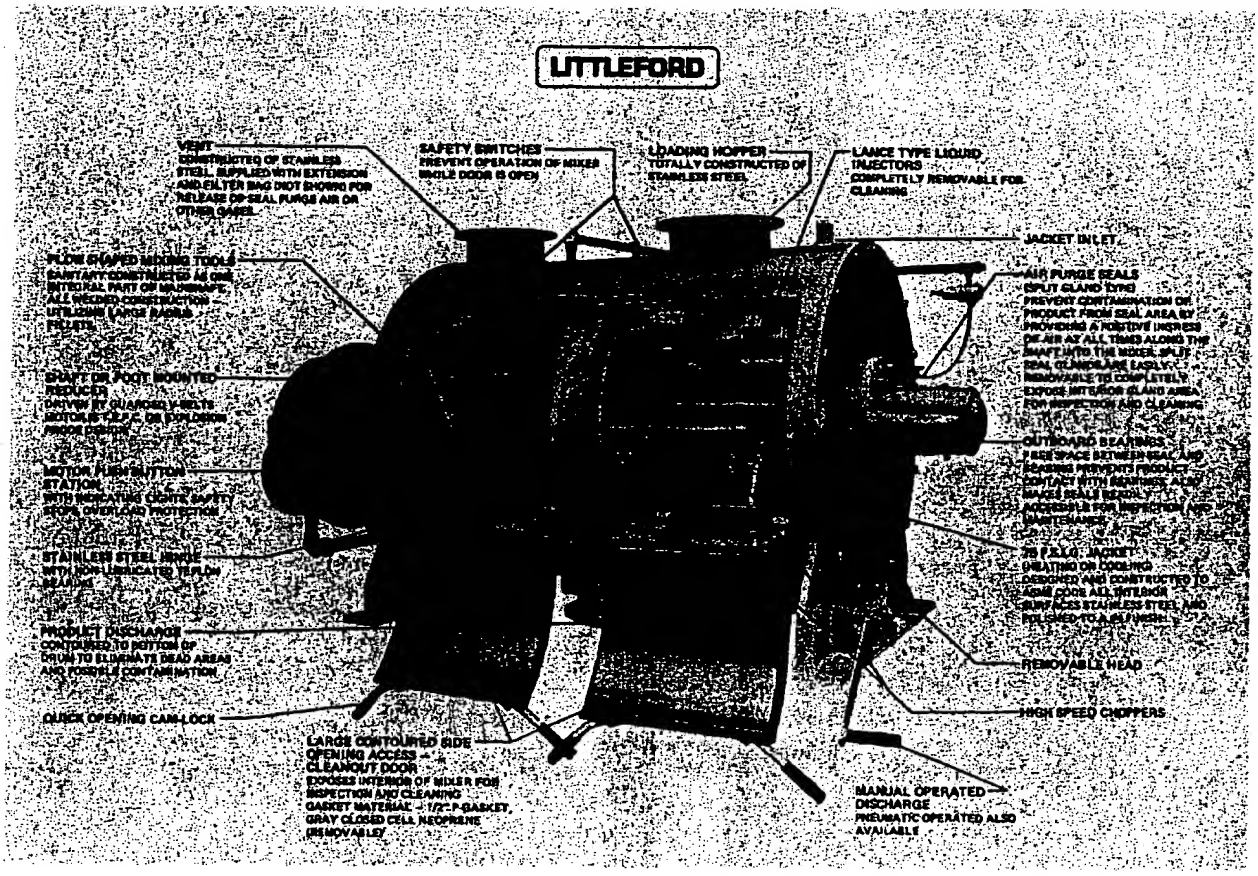

FIG. 11-14. *The Littleford Lodige mixer. (Courtesy of Littleford Brothers, Florence, KY.)*

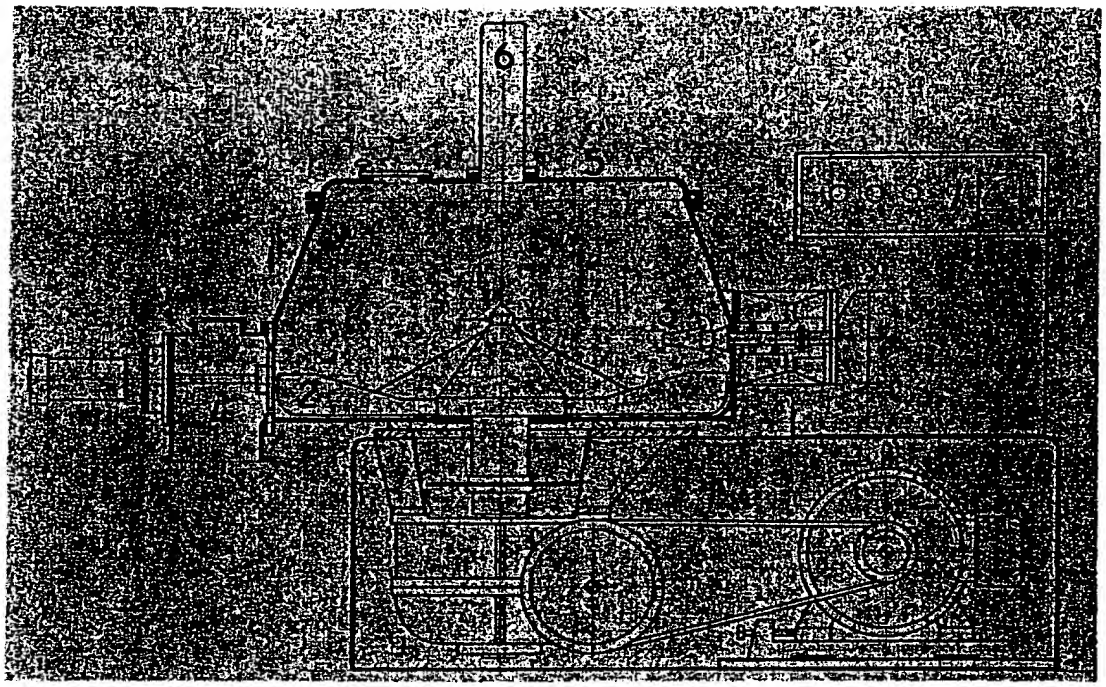

FIG. 11-15. *Schematic diagram of the Diosna mixer. (1) Mixer bowl. (2) High-speed mixer blade. (3) High-speed chopper blade. (4) Pneumatic discharge port. (5) Mixed lid. (6) Exhaust air sleeve. (7) Mixer control panel. (Courtesy of Dierks and Sohne, Osnabrück, West Germany.)*

ing bowl, which powers the blade. The blade is specially constructed to discourage material from getting under it. The mixer also contains a high-speed chopper blade (3), which functions as a lump and agglomerate breaker. A pneumatic discharge port (4) provides the unit with automatic discharge. The unit is provided with a lid (5) and the larger units employ a counterweight to assist in raising and lowering the lid. The lid has three openings: one to accommodate a spray nozzle, a second larger opening for an air exhaust sleeve (6), and a third opening for a viewing port. The units are also equipped with an ammeter on the control panel, (7) which may be employed to determine the end point of granulation operations. Typical time sequences for the use of a Diosna mixer are as follows: mixing, 2 min or less; granulating, 8 min or less; discharge, 1 min with the discharge capable of being preset when the pneumatic discharge system is in place.

Figure 11-16 describes the Littleford MGT mixer/granulator, which has been developed to meet granulation needs more specifically. For comparison, the horizontal configuration of the Lodige unit (Fig. 11-15) has been rotated 90° to a vertical configuration, the drum assembly has been converted to a bowl assembly, and a discharge port has been added to facilitate emptying and cleaning of the bowl. The principle of operation, however, is the same as that described previously for the Diosna mixer.

When a high-shear solids mixer is used in a production operation, mounting the mixer in a position that allows the bowl from a fluid bed dryer to be placed under the mixer facilitates materials transfer. Most fluid bed dryers for production operations have wheeled assemblies to facilitate materials transfer to and from the fluid bed unit. Since wet granular material may resist transfer by air conveyor systems such as the Vacumax, a gravity type of transfer provision may be especially helpful. The need to raise the equipment to an appropriate working height in order to discharge directly into a bowl of a fluid bed dryer is not regarded as a major disadvantage, provided that powder can be conveniently charged into the unit when it is in a raised position.

Figure 11-17 illustrates the Gral mixer/granulator. This equipment is a modification of the industrial planetary mixers. The difference between the Gral mixer/granulator and a standard planetary mixer is that the new unit contains two mixing devices. A large mixing arm is shaped to the rounded configuration of the bowl and provides the large-scale mixing motion on the powder. A smaller chopper blade enters off-center from the mixing arm and is located above it. The larger mixing blade and a second-

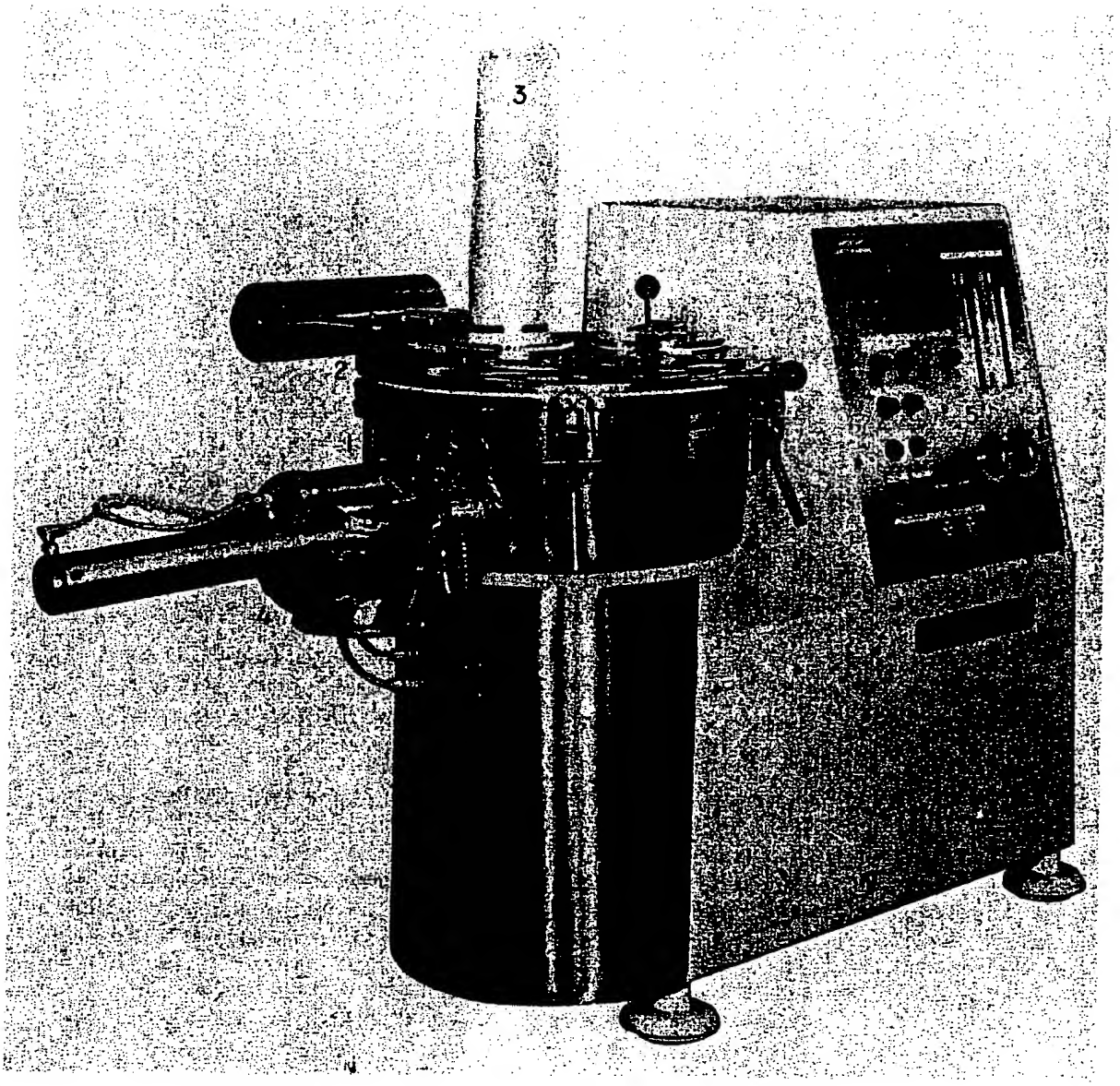

FIG. 11-16. *The Littleford MGT mixer-granulator. (1) Bowl. (2) Lid with counter weight. (3) Exhaust sleeve. (4) Discharge port. (5) Control panel. (Courtesy of Littleford Brothers, Florence, KY.)*

ary chopper blade system is therefore similar to the Lodige and Diosna units previously described. The difference, however, is that the Gral unit has the configuration of a planetary top-entering mixer. The mixing bowl may be loaded at floor level, as in Figure 11-17, and then raised to the mixing position by the hydraulic bowl elevator cradle. The bowl is brought into contact with a cover providing a tight seal. An advantage of the unit is that it may be discharged by its hydraulic port while in the raised position, offering sufficient space for a container to be placed beneath the discharged port. The entire mixer unit does not have to be elevated to provide this vertical discharge distance as is necessary with the two previously mentioned high-shear mixers. Another advantage of the unit is that the main mixing blade is not a part of the bowl, thus making cleanup easier. Fluid may be injected into the mixer bowl. The equipment is available with time control.

Tablet Design and Formulation

The three basic methods of tablet manufacture have been previously detailed, the desirable properties and required features of granulations and tablets defined, and the interrelationships between many of these properties and the processing and machine variables noted. Regardless

FIG. 11-17. *The Gral mixer-granulator. (1) Mixing arm. (2) Bowl. (3) Chopper blade. (4) Bowl cover. (5) Hydraulic discharge port. (6) Mixer control panel. (7) Bowl elevator cradle. (Courtesy of Machines Collette, Wheeling, IL.)*

of how tablets are manufactured, conventional oral tablets for ingestion usually contain the same classes of components in addition to the active ingredients, which are one or more agents functioning as (1) a diluent, (2) a binder or an adhesive, (3) a disintegrant, and (4) a lubricant. Some tablet formulations may additionally require a flow promoter. Other more optional components include colorants, and in chewable tablets, flavors and sweeteners. All nondrug components of a formula are termed excipients.

Diluents

Diluents are fillers designed to make up the required bulk of the tablet when the drug dosage itself is inadequate to produce this bulk. The dose of some drugs is sufficiently high that no filler is required (e.g., aspirin and certain antibiotics). Round tablets for ingestion are usually in a size range of 3/16 to ½ inch. Tablets below 3/16 inch may be difficult for the elderly to handle, and those larger than ½ inch become difficult to swallow. This provides a tablet weight range of perhaps 120 to 700 mg for standard density organic materials. By using oval tablets, which may be easier to swallow, tablets weighing up to 800 mg or more may be produced. Tablet formulations may contain a diluent for secondary reasons: to provide better tablet properties such as improved cohesion, to permit use of direct compression manufacturing, or to promote flow.

Regardless of why a diluent is selected, diluents and *all* other tablet excipients must meet certain criteria in the formulation. These include the following:

1. They must be nontoxic and acceptable to the regulatory agencies in all countries where the product is to be marketed.
2. They must be commercially available in an acceptable grade in all countries where the product is to be manufactured.
3. Their cost must be acceptably low.
4. They must not be contraindicated by themselves (e.g., sucrose) or because of a component (e.g., sodium) in any segment of the population.
5. They must be physiologically inert.
6. They must be physically and chemically stable by themselves and in combination with the drug(s) and other tablet components.
7. They must be free of any unacceptable microbiologic "load."
8. They must be color-compatible (not produce any off-color appearance).
9. If the drug product is also classified as a food, (certain vitamin products), the diluent and other excipients must be approved direct food additives.
10. They must have no deleterious effect on the bioavailability of the drug(s) in the product.

There are cited cases of pharmaceutical manufacturers actually producing products in which an excipient reduced the bioavailability of a drug, or in which chemical incompatibilities existed. The former situation occurred with the marketing of an antibiotic that utilized a calcium salt as the diluent. The tetracycline product made with a calcium phosphate filler had less than half the bioavailability of the standard product.[33] Divalent and trivalent cations form insoluble complexes and salts with a number of amphoteric or acid functionality antibiotics, which greatly reduces their absorption (which is

also why milk should not be coadministered with these drugs). A classic case of a chemical incompatibility that went unrecognized for several years was the interaction of certain amine drugs with the commonly used diluent lactose, in the presence of a metal stearate lubricant (such as magnesium stearate); the resulting tablets were gradually discolored with time.[34-35] Tablet formulators should remember that physical and chemical interactions between formulation components may be promoted by the intimate contact between potential reactants that are tightly compressed together in a tablet compact. Thus, materials that are capable of forming a eutectic mixture, for example, may pose no problem when loosely packed as a powder in a capsule, while the same formulation when compressed in a tablet forms a compact that quickly softens and becomes unacceptable.

Table 11-4 lists some of the commonly used tablet diluents. Note that several of the diluents listed exist as hydrates (dibasic calcium phosphate and calcium sulfate). Diluents that exist in their common salt form as hydrates, containing appreciable bound water as water of crystallization, may nevertheless be excellent for very water-sensitive drugs, provided that the bound water is not released under any elevated storage condition to which the product might be exposed. Dibasic calcium phosphate and calcium sulfate have the advantages of possessing low concentrations of unbound moisture and having a low affinity for atmospheric moisture. These are required features for any excipient material to be combined with a water-sensitive drug. The bound water of calcium sulfate is not released until a temperature of approximately 80°C is reached. Such bound water is usually unavailable for chemical reaction. Such excipients containing tightly bound water but having a low remaining moisture demand may be vastly superior to an anhydrous diluent, which has a moderate to high moisture demand.

Lactose is the first diluent listed in Table 11-4 because it is still the most widely used diluent in tablet formulation. Lactose is an excipient that has no reaction with most drugs, whether it is used in the hydrous or anhydrous form. Anhydrous lactose has the advantage over lactose in that it does not undergo the Maillard reaction, which can lead to browning and discoloration with certain drugs, as noted previously. The anhydrous form, however, picks up moisture when exposed to elevated humidity. Such tablets may have to be carefully packaged to prevent moisture exposure. When a wet granulation process is employed, the hydrous form of lactose should generally be used. Two grades of lactose are commonly available commercially: a 60- to 80-mesh (coarse) and an 80- to 100-mesh (regular) grade. In general, lactose formulations show good drug release rates, their granulations are readily dried, and the tablet disintegration times of lactose tablets are not strongly sensitive to variations in tablet hardness. Lactose is a low-cost diluent, but it may discolor in the presence of amine drug bases or salts of alkaline compounds.

Spray-dried lactose is one of several diluents now available for direct compression following mixing with the active ingredient, and possibly, a disintegrant and a lubricant. If this form of lactose is allowed to dry out and the moisture content falls below the usual 3% level, the material loses some of its direct compressional characteristics. In addition to its direct compression properties, spray-dried lactose also has good flow characteristics. It can usually be combined with as much as 20 to 25% of active ingredient without losing these advantageous features. Spray-dried lactose is especially prone to darkening in the presence of excess moisture, amines, and other compounds, owing to the presence of a furaldehyde. A neutral or acid lubricant should be used when spray-dried lactose is employed.

Starch, which may come from corn, wheat or potatoes, is occasionally used as a tablet diluent. The USP grade of starch, however, has four flow and compression characteristics and possesses a high typical moisture content of between 11 and 14%. Specially dried types of starch that have a standard moisture level of 2 to 4% are available, but at a premium price. Use of such starches in wet granulation is wasteful since their moisture levels increase to 6 to 8% following moisture exposure.

Various directly compressible starches are now available commercially. Sta-Rx 1500 is one such free-flowing, directly compressible starch; it may be used as a diluent, binder, and/or disintegrating agent. Since it is self-lubricating, it may be compressed alone, but when combined with as little as 5 to 10% of drug, it typically requires addition of a lubricant, and possibly a flow promoter such as 0.25% of a colloidal silicone dioxide. Sta-Rx 1500 contains about 10% moisture and is reportedly prone to softening when combined with excessive amounts (more than 0.5%) of magnesium stearate.

Two hydrolyzed starches are Emdex and Celutab, which are basically 90 to 92% dextrose and about 3 to 5% maltose. They are free-flowing and directly compressible. These materials may be used in place of mannitol in chewable tablets because of their sweetness and smooth feeling in the mouth. These materials contain

about 8 to 10% moisture and may increase in hardness after compression.

Dextrose is also used as a tablet diluent. It is available from one supplier under the name Cerelose and comes in two forms: as a hydrate, and in anhydrous form for when low moisture contents are required. Dextrose is sometimes combined in formulation to replace some of the spray-dried lactose, which may reduce the tendency of the resulting tablets to darken.

Mannitol is perhaps the most expensive sugar used as a tablet diluent, but because of its negative heat of solution, its slow solubility, and its pleasant feeling in the mouth, it is widely used in chewable tablets. It is relatively nonhygroscopic and can be used in vitamin formulation, in which moisture sensitivity may be a problem. Mannitol formulations typically have poor flow characteristics and usually require fairly high lubricant levels.

Sorbitol is an optical isomer of mannitol and is sometimes combined in mannitol formulations to reduce diluent cost; however, sorbitol is hygroscopic at humidities above 65%. Both of these sugars have a low caloric content and are noncariogenic.

Sucrose, or sugar, and various sucrose-based diluents are employed in tablet making. Some manufacturers avoid their use in products that would subject a diabetic to multiple gram quantities of sugar. Some of the sucrose-based diluents have such tradenames as Sugartab (90 to 93% sucrose plus 7 to 10% invert sugar), DiPac (97% sucrose plus 3% modified dextrins), and Nu Tab (95% sucrose and 4% invert sugar with a small amount of corn starch and magnesium stearate). All of these diluents are available for direct compression, and some are also employed, with or without mannitol, in chewable tablets. All have a tendency to pick up moisture when exposed to elevated humidity.

Microcrystalline cellulose, often referred to by the tradename Avicel, is a direct compression material. Two tablet grades exist: PH 101 (powder) and PH 102 (granules). The flow properties of the material are generally good, and the direct compression characteristics are excellent. This is a somewhat unique diluent in that while producing cohesive compacts, the material also acts as a disintegrating agent. It is, however, a relatively expensive material when used as a diluent in high concentration and is thus typically combined with other materials. As in the case of starch, microcrystalline cellulose is often added to tablet formulation for several possible functions. It is a commonly employed excipient.

While a careful search of the literature reveals over 50 chemicals that have been evaluated and advocated as tablet diluents, those listed in Table 11-4 probably represent 80 to 90% of currently used diluents.

Binders and Adhesives

These materials are added either dry or in liquid form during wet granulation to form granules or to promote cohesive compacts for directly compressed tablets. Acacia and tragacanth are natural gums (listed in Table 11-4), and are employed in solutions ranging from 10 to 25% concentration, alone or in combination. These materials are much more effective when they are added as solutions in the preparation of granulations than when they are added dry to a direct compression formula. These natural gums have the disadvantage of being variable in their composition and performance based on their natural origin, and they are usually fairly heavily contaminated with bacteria. When these materials are used, their wet granulation masses should be quickly dried at a temperature above 37° to reduce microbial proliferation.

Gelatin is a natural protein and is sometimes used in combination with acacia. It is a more consistent material than the two natural gums, is easier to prepare in solution form, and forms tablets equally as hard as acacia or tragacanth. Starch paste has historically been one of the most common granulating agents. It is prepared by dispersing starch into water, which is then heated for some prescribed time. During the heating, the starch undergoes hydrolysis to dextrin and to glucose. A properly made paste is translucent rather than clear (which would indicate virtually complete conversion to glucose) and produces cohesive tablets that readily disintegrate when properly formulated. Liquid glucose, which is a 50% solution in water, is a fairly common wet granulating agent. Its properties are similar to those of sucrose solutions, which are commonly employed in concentrations between 50 and 74%. These sugar solutions are capable of producing wet granulations, which when tabletted, produce hard but somewhat brittle compacts. These materials have the advantage of being low-cost adhesives. Unless the sugar solutions are highly concentrated, bacterial proliferation may be a problem.

Modified natural polymers, such as the alginates and cellulose derivatives (methylcellulose, hydroxypropyl methylcellulose, and hydroxypropyl cellulose), are common binders and adhesives. Used dry for direct compression, they have some binder capabilities, while their aqueous solutions have adhesive properties. Hydroxypropyl cellulose may also be used as an alcohol

solution to provide an anhydrous adhesive. Ethylcellulose may be used only as an alcoholic solution, and it may be expected to retard disintegration and dissolution time of drugs in the resulting tablets when wet granulation is employed. Polyvinylpyrrolidone is a synthetic polymer that may be used as an adhesive in either an aqueous solution or alcohol. It also has some capabilities as a dry binder.

Disintegrants

A disintegrant is added to most tablet formulations to facilitate a breakup or disintegration of the tablet when it contacts water in the gastrointestinal tract. Disintegrants may function by drawing water into the tablet, swelling, and causing the tablet to burst apart. Such tablet fragmentation may be critical to the subsequent dissolution of the drug and to the attainment of satisfactory drug bioavailability. Starch USP and various starch derivatives are the most common disintegrating agents. They also have the lowest cost. Starch is typically used in a concentration range of 5 to 20% of tablet weight. Such modified starches as Primogel and Explotab, which are low substituted carboxylmethyl starches, are used in lower concentrations (1 to 8%, with 4% usually reported as optimum). Various pregelatinized starches are also employed as disintegrants, usually in a 5% concentration.

Clays such as Veegum HV and bentonite have been used as disintegrants at about a 10% level. Such use of these materials is limited unless the tablets are colored, since the clays produce an off-white appearance. The clays are typically less effective as disintegrants than some of the newer modified polymers and starches, which can increase in volume in the presence of water by 200 to 500%. The disintegrating characteristics of microcrystalline cellulose have been reported previously in this chapter; however, in the cellulose class, a new material known as Ac-Di-Sol is now available and is effective in low concentration levels. It is an internally cross-linked form of sodium carboxymethylcellulose. Another cross-linked polymer that is available as a disintegrant is cross-linked polyvinylpyrrolidone.

Lubricants, Antiadherents, and Glidants

These three classes of materials are typically described together because they have overlapping functions. A material that is primarily described as an antiadherent is typically also a lubricant, with some glidant properties as well. The differentiation between these terms is as follows: Lubricants are intended to reduce the friction during tablet ejection between the walls of the tablet and the walls of the die cavity in which the tablet was formed. Antiadherents have the purpose of reducing sticking or adhesion of any of the tablet granulation or powder to the faces of the punches or to the die wall. Glidants are intended to promote flow of the tablet granulation or powder materials by reducing friction between the particles.

In addition to the lubricants listed in Table 11-4, hydrocarbon oils such as mineral oil have been employed by application to granulation as a fine spray, either directly or in a solvent solution. The problem with using this type of lubricant is the production of oil spots. The most widely used lubricants have been stearic acid and various stearic acid salts and derivatives. Calcium and magnesium stearate are the most common salts employed. Stearic acid is a less effective lubricant than these salts and also has a lower melting point. Talc is probably the second most commonly used tablet lubricant, historically. Most talc samples are found to contain trace quantities of iron, and talc should be considered carefully in any formulation containing a drug whose breakdown is catalyzed by the presence of iron. The higher-molecular-weight polyethylene glycols and certain polymeric surfactants have been used as water-soluble lubricants. These materials are much less effective as lubricants, however, than the materials previously cited. Since lubrication is basically a coating process, the finer the particle size of the lubricant, the more effective the lubricant action is likely to be.

As previously noted, most of the materials listed as lubricants, with the possible exception of those that are water-soluble, also function as antiadherents. Talc, magnesium stearate, and starch as well as starch derivatives possess antiadherent properties. In addition, various colloidal silicas have been used as antiadherents.

Materials used as glidants, or flow promoters, are typically talc at a 5% concentration, corn starch at a 5 to 10% concentration, or colloidal silicas such as Cab-O-Sil, Syloid, or Aerosil in 0.25 to 3% concentrations.

Colors, Flavors and Sweeteners

The use of colors and dyes in tablet making has served three purposes over the years: disguising of off-color drugs, product identification, and production of a more elegant product. With the continual decertification of many synthetic

dyes, pharmaceutical manufacturers are becoming quite concerned as to how future tablet formulations will be colored. The availability of natural vegetable colors is limited, and these colors are often unstable. Two forms of color have typically been used in tablet preparation. These are the FD&C and D&C dyes—which are applied as solutions, typically in the granulating agent—and the lake forms of these dyes. Lakes are dyes that have been absorbed on a hydrous oxide and usually are employed as dry powders for coloring. In addition to concerns regarding possible delisting in the future, several other precautions should be considered when colors are employed. When using water-soluble dyes, pastel shades usually show the least mottling from uneven distribution in the final tablet. When wet granulation is employed, care should be taken to prevent color migration during drying. In any colored tablet, the formulation should be checked for resistance to color changes on exposure to light. Various artificial light sources are available that simulate the ultraviolet spectrum of sunlight. Methods of quantifying color are given earlier in the chapter under the heading, "Organoleptic Properties."

Flavors are usually limited to chewable tablets or other tablets intended to dissolve in the mouth. In general, flavors that are water-soluble have found little acceptance in tablet making because of their poor stability. Flavor oils are added to tablet granulations in solvents, are dispersed on clays and other absorbents, or are emulsified in aqueous granulating agents. Various dry flavors for use in pharmaceutical products are also available from flavor suppliers. Usually, the maximum amount of oil that can be added to a granulation without influencing its tabletting characteristics is 0.5 to 0.75%.

The use of sweeteners is primarily limited to chewable tablets to exclude or limit the use of sugar in the tablets. Various sugars used as tablet excipients have been described earlier. Mannitol is reportedly about 72% as sweet as sucrose. Until recently, saccharin was the only artificial sweetener available. This material is about 500 times sweeter than sucrose. Its major disadvantages are that it has a bitter aftertaste and has been reported to be carcinogenic. A new artificial sweetener that is expected to largely replace saccharin is aspartame. The primary disadvantage of aspartame is its lack of stability in the presence of moisture. When aspartame is used in a formulation, e.g., a chewable tablet with hygroscopic components, it will be necessary to determine its stability under conditions in which the product can adsorb atmospheric moisture.

Examples of tablet formulations are shown in the Appendices to this chapter. Not only do the formulations illustrate the use of common ingredients, but they also illustrate the use of the ingredients in tablets to be made by wet granulation, dry granulation, and direct compression processes.

It has previously been noted that while the excipients are the inactive part of a tablet formulation, they have a direct influence on the quality and effectiveness of the final product. Figure 11-18 describes, for example, the influence of compression force on disintegration time for various direct compression materials. Some materials have a maximum disintegration time of no higher than 200 to 250 sec, regardless of the compression force applied over the range studied. One material rapidly increased in disintegration time to over 500 sec at a compression force of less than 1000 kg. Similar relationships between important tablet properties and processing characteristics can be shown for many other tablet excipients.

Another important consideration that many pharmaceutical formulators must consider in tablet formulation is the worldwide acceptability of their formulation components. An excipient used in the United States, for example, may not be permitted in a major market area such as Japan or Europe, or vice-versa. Companies with major international markets strive to have tablet formulations that are equally acceptable around the world and that contain components that are not likely to be delisted in any country.

Types and Classes of Tablets

Tablets are classified by their route of administration or function, by the type of drug delivery system they represent within that route, and by their form and method of manufacture. Table 11-5 lists the various classes of tablets, with the primary classification being the route of administration or function.

Tablets Ingested Orally

Well over 90% of the tablets manufactured today are ingested orally. Orally ingested tablets are designed to be swallowed intact, with the exception of chewable tablets.

Compressed Tablets or Standard Compressed Tablets. This category refers to standard uncoated tablets made by compression and employing any of the three basic methods of manufacture: wet granulation, double compaction, or direct compression. Tablets in this category are usually intended to provide rapid disin-

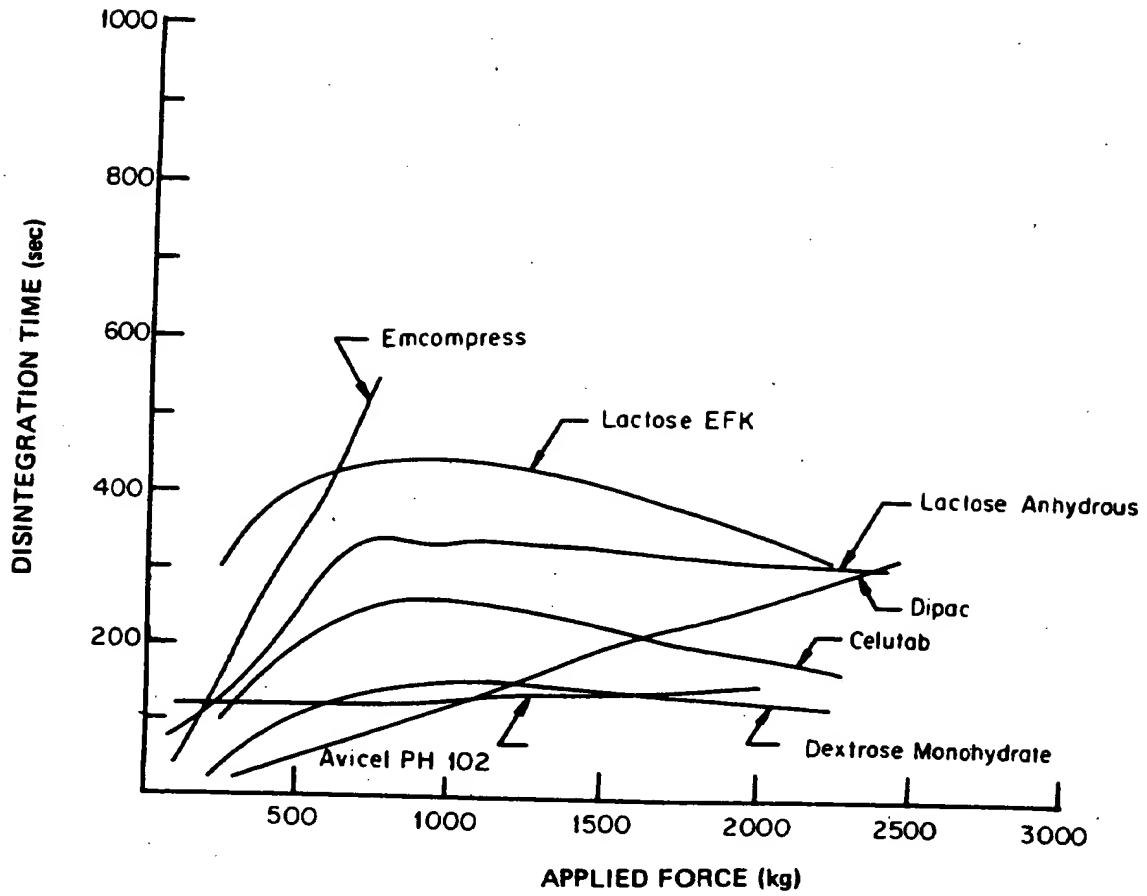

FIG. 11-18. *Disintegration time vs. applied force for tablets prepared from various direct compression diluents. (Reprinted from Banker, G. S., Peck, G. E., and Baley, G.: Tablet formulation and design. In Pharmaceutical Dosage Forms: Tablets. Vol. 1. Edited by H. Lieberman and L. Lachman. Marcel Dekker, New York, 1980, p. 75, by courtesy of Marcel Dekker, Inc.)*

tegration and drug release. Most tablets containing drugs intended to exert a local effect in the gastrointestinal tract are of this type. These drugs are typically water-insoluble and include such therapeutic categories as the antacids and adsorbents. Other drugs in this group are intended to produce a systemic effect. These drugs have some aqueous solubility, dissolve from the tablet and disintegrated tablet fragments in GI contents, and are then absorbed and distributed in the body. As described earlier in this chapter, proper disintegration of the tablet and deaggregation of the tablet fragments or granular particles are often critical to the proper performance of the dosage form. The locally acting drugs mentioned perform in accordance with their state of deaggregation, since adsorbents and antacids both involve surface activity that increases as their surface area increases. Dissolution is also a surface-related phenomenon, with dissolution rates increasing as a drug's surface area is increased. Thus, tablet breakup and particle deaggregation is also important for drugs designed to produce systemic effects. As the solubility of the drug decreases, especially with acidic drug moieties that are absorbed best in the upper GI tract, rapid tablet disintegration becomes increasingly important, even critical, for this tablet category.

Multiple Compressed Tablets. There are two classes of multiple compressed tablets: layered tablets and compression-coated tablets. Both types may be either two-component or three-component systems: two- or three-layer tablets, a tablet within a tablet, or a tablet within a tablet within a tablet. Both types of tablets usually undergo a light compression as each component is laid down, with the main compression being the final one. Tablet machine production speeds for multiple compressed tablets are appreciably slower than for standard compressed tablets, especially in the case of compression-coated tablets.

Tablets in this category are usually prepared for one of two reasons: to separate physically or chemically incompatible ingredients, or to pro-

TABLE 11-5. *Types and Classes of Tablets*

Oral Tablets for Ingestion
Compressed tablets or standard compressed tablets (CT)
Multiple compressed tablets (MCT)
Layered tablets
Compression-coated tablets
Repeat-action tablets
Delayed-action and enteric coated tablets
Sugar- and chocolate-coated Tablets
Film-coated tablets
Chewable tablets
Tablets Used in the Oral Cavity
Buccal tablets
Sublingual tablets
Troches and lozenges
Dental cones
Tablets Administered by Other Routes
Implantation tablets
Vaginal tablets
Tablets Used to Prepare Solutions
Effervescent tablets
Dispensing tablets (DT)
Hypodermic tablets (HT)
Tablet triturates (TT)

duce repeat-action or prolonged-action products. In some cases, a two-layer tablet may provide adequate surface separation of reactive ingredients; if complete physical separation is required for stability purposes, the three-layer tablet may be employed. The layered tablet is preferred to the compression-coated tablet; surface contact between layers is lessened, and production is simpler and more rapid.

Multiple compressed tablets readily lend themselves to repeat-action products, wherein one layer of the layered tablet or the outer tablet of the compression-coated tablet provides the initial dose, rapidly disintegrating in the stomach. The other layer or the inner tablet is formulated with components that are insoluble in gastric media but are released in the intestinal environment. The shortcoming of this category of dosage form for repeat-action products is that its performance is highly dependent on gastric emptying. If the second layer or core tablet quickly leaves the stomach following release of the initial fast-release dose, an entirely different blood level profile results than if there is a several-hour or longer delay before the second fraction is emptied. It is probably for this reason that relatively few repeat-action or controlled-release products using this approach are marketed.

Rep at-Acti n Tablets. The mode of operation of repeat-action tablets, and their limitations based on uncontrolled and unpredictable gastric emptying, have just been mentioned. In addition to multiple compressed tablets being used for this effect, sugar-coated tablets may also be employed. The core tablet is usually coated with shellac or an enteric polymer so that it will not release its drug load in the stomach. The second dose of drug is then added in the sugar coating, either in solution in the sugar syrup or as a part of the dusting powder added for rapid coat buildup. More uniform drug addition occurs if the drug is in solution or fine suspension in the sugar solution, especially if an automated-spray sugar-coating operation is employed. Even so, the coating operation will probably require interruption one or more times while the partially coated tablets are assayed to establish that the correct amount of drug has been applied in the coating.

Delayed-Action and Enteric Coated Tablets. The delayed-action tablet dosage form is intended to release a drug after some time delay, or after the tablet has passed through one part of the GI tract into another. The enteric coated tablet is the most common example of a delayed-action tablet product. All enteric coated tablets (which remain intact in the stomach but quickly release in the upper intestine) are a type of delayed-action tablet. Not all delayed-action tablets are enteric or are intended to produce the enteric effect. In veterinary product development, tablets may be designed to pass through the stomach (or several stomachs) of an animal or through all or most of the small intestine before releasing—or even into the cecum or large bowel, as in the case of treating worm parasites located in this lower region. In a human drug application, a product may be designed to pass through the stomach intact and then release gradually for several hours or longer in the intestines.

The compendial specifications for an enteric coated tablet are that all of the six tablets placed in separate tubes of the USP disintegration apparatus (using discs) remain intact after 30 min of exposure in simulated gastric fluid at 37°C ± 2°C and then disintegrate within the time specified for that product's monograph, plus 30 min. If one or two tablets fail to disintegrate completely in the intestinal fluid, the test is repeated on 12 additional tablets; not less than 16 of the total 18 tablets tested must disintegrate completely. Prior to gastric exposure, the tablets

are immersed in water at room temperature for 5 minutes.

The coatings that are used today to produce enteric effects are primarily mixed acid functionality and acid ester functionality synthetic or modified natural polymers. Cellulose acetate phthalate has the longest history of use as an enteric coating. More recently, polyvinyl acetate phthalate and hydroxypropyl methylcellulose phthalate have come into use. All three polymers have the common feature of containing the dicarboxylic acid, phthalic acid, in partially esterfied form. These polymers, being acid esters, are insoluble in gastric media that have a pH of up to about 4; they are intended to hydrate and begin dissolving as the tablets leave the stomach, enter the duodenum (pH of 4 to 6), and move further along the small intestine, where the pH increases to a range of 7 to 8. The primary mechanism by which these polymers lose their film integrity, thereby admitting intestinal fluid and releasing drug, is ionization of the residual carboxyl groups on the chain and subsequent hydration. The presence of esterases in the intestinal fluid that break down ester linkages of the polymer chains may also play some role, as may surface activity effects of bile salts and other components in bile that enter the upper small intestine via the bile duct.

Enteric coatings are employed for a number of therapeutic, safety, and medical reasons. Some drugs are irritating when directly exposed to the gastric mucosa, including aspirin and strong electrolytes such as NH_4Cl. While for most people the occasional aspirin tablet may not cause irritation, those on daily doses of aspirin, such as arthritics, may find gastric upset a major problem. Enteric coating is one method of reducing or eliminating irritation from such drugs. There are other drugs that if released in the stomach may produce nausea and vomiting. The low pH of the stomach destroys other drugs (for example, erythromycin), and hence enteric coating may be necessary to bring the drug through that environment to the more neutral intestinal contents. Yet another reason for enteric coating may be the desire to release the drug undiluted and in the highest concentration possible within the intestine. (Examples are intestinal antibacterial or antiseptic agents and intestinal vermifuges.) As in the case of repeat-action and other controlled-release dosage forms, the influence of altering the release profile of the drug on total drug bioavailability, distribution, and pharmacokinetics must be investigated.

Sugar- and Choc late-Coated Tablets. Chocolate-coated tablets are nearly a thing of the past. They are too easily mistaken for candy by children. Sugar-coated tablets suffer the same disadvantage. Their primary historical role was to produce an elegant, glossy, easy-to-swallow tablet dosage form. Also, they permit separation of incompatible ingredients between coating and core, and this fact has been widely utilized in preparing many multivitamin and multivitamin mineral combinations. The process as originally developed was time-consuming and required skilled coating artisans to be conducted properly. Earlier sugar coatings typically doubled tablet weight. Today, water-soluble polymers are often incorporated in the sugar solution, automated-spray coating equipment is employed, and high-drying-efficiency side-vented coating pans are used. The result is that the coatings are more elastic and mechanically stable, coat weight may be 50% or less of the core weight, and the process may be completed in a day or less.

Film-Coated Tablets. Film-coated tablets were developed as an alternative procedure to the preparation of coated tablets in which drug was not required in the coating. The initial film-coating compositions employed one or more polymers, which usually included a plasticizer for the polymer and possibly a surfactant to facilitate spreading, all delivered to the tablets in solution from an organic solvent. The film-coating process was an attractive tablet coating method since it permitted the completion of the tablet coating operation in a period of one or two hours. An airless spray coating procedure was typically employed for such film-coating compositions, using either conventional coating pans or side-vented equipment. During the decade of the 1970s, several factors began to make solvent-based film coating less attractive. These factors were the increase in cost of the organic solvents, OSHA restrictions on worker exposure to solvent vapors, and EPA limitations on solvent vapor discharge to the atmosphere. As a result of these influences, many companies have now converted their earlier film-coating process to a totally aqueous-based procedure. Polymers such as hydroxypropyl cellulose and hydroxypropyl methylcellulose, which are dissolved in water with an appropriate plasticizer, are now widely used to produce immediate-release film coatings. The recent development of a colloidal dispersion of ethylcellulose in water also makes it possible to produce slow- or controlled-release film coatings without the use of organic solvents. A 30% ethylcellulose dispersion is marketed under the trade name Aquacoat by the FMC Corporation.

Film-coated tablets offer a number of advantages over sugar-coated tablets. These advan-

tages include better mechanical strength of the coating based on the elasticity and flexibility of the polymer coating, little increase in tablet weight, the ability to retain debossed markings on a tablet through the thin film coating, the avoidance of sugar, which is contraindicated in the diets of a significant segment of the population, and the employment of a process that may be continuous, or that readily lends itself to automation. The primary disadvantage of film coating compared with sugar coating is that it is difficult to produce film-coated tablets that match the physical appearance and elegance of the sugar-coated product. Film coating in the future will assume increasing importance as a means of controlling drug delivery release rates from both tablets and bead particles as well as from drug crystals. Film-coated tablets, which are basically tasteless, also offer the advantage over sugar-coated tablets of being less likely to be mistaken for candy.

Chewable Tablets. Chewable tablets are intended to be chewed in the mouth prior to swallowing and are not intended to be swallowed intact. The purpose of the chewable tablet is to provide a unit dosage form of medication which can be easily administered to infants and children or to the elderly, who may have difficulty swallowing a tablet intact. The types of sugars and other components employed in chewable tablets have been designated in this chapter under the heading "Table Design and Formulation." The most common chewable tablet on the market is the chewable aspirin tablet intended for use in children. Bitter or foul-tasting drugs are not good candidates for this type of tablet, and this fact restricts the use of the chewable tablet dosage form. Many antacid tablet products are of the chewable type. The chewable tablet offers two major advantages to the delivery of a solid antacid dosage form. First, the dose of most antacids is large, so that the typical antacid tablet would be too large to swallow. Second, as noted previously, the activity of an antacid is related to its particle size. If the tablet is chewed prior to swallowing, better acid neutralization may be possible from a given antacid dose.

Tablets Used in the Oral Cavity

Buccal and Sublingual Tablets. These two classes of tablets are intended to be held in the mouth, where they release their drug contents for absorption directly through the oral mucosa. These tablets are usually small and somewhat flat, and are intended to be held between the cheek and teeth or in the cheek pouch (buccal tablets), or beneath the tongue (sublingual tablets). Drugs administered by this route are intended to produce systemic drug effects, and consequently, they must have good absorption properties through the oral mucosa. Drug absorption from the oral mucosa into the bloodstream leads directly to the general circulation. Drug absorption from the gastrointestinal tract leads to the mesenteric circulation, which connects directly to the liver via the portal vein. Thus, drug absorption from the oral cavity avoids first-pass metabolism. The oral route of administration from these two classes of tablet dosage form thus offers several possible advantages: The gastric environment, where decomposition may be extensive (for certain steroids and hormones), may be avoided for drugs that are well absorbed in the mouth. A more rapid onset of drug action occurs than for tablets that are swallowed (an advantage with vasodilators given by this route). The first-pass effect may be avoided as noted previously, and for certain drugs (e.g., methyltestosterone), the nausea produced when the product is swallowed is avoided.

Buccal and sublingual tablets should be formulated with bland excipients, which do not stimulate salivation. This reduces the fraction of the drug that is swallowed rather than being absorbed through the oral mucosa. In addition, these tablets should be designed not to disintegrate but to slowly dissolve, typically over a 15- to 30-min period, to provide for effective absorption.

Troches and Lozenges. These are two other types of tablets used in the oral cavity, where they are intended to exert a local effect in the mouth or throat. These tablet forms are commonly used to treat sore throat or to control coughing in the common cold. They may contain local anesthetics, various antiseptic and antibacterial agents, demulcents, astringents, and antitussives. Lozenges were originally termed pastilles, but are more commonly called cough drops. They are usually made with the drug incorporated in a flavored hard-candy sugar base. Lozenges may be made by compression but are usually formed by fusion or by a candy-molding process. Troches, on the other hand, are manufactured by compression as are other tablets. These two classes of tablets are designed not to disintegrate in the mouth but to dissolve or slowly erode over a period of perhaps 30 min or less.

Dental Cones. Dental cones are a relatively minor tablet form that are designed to be placed in the empty socket remaining following a tooth extraction. Their usual purpose is to prevent the multiplication of bacteria in the socket following such extraction by employing a slow-releasing

antibacterial compound, or to reduce bleeding by containing an astringent or coagulant. The usual vehicle of these tablets is sodium bicarbonate, sodium chloride, or an amino acid. The tablet should not be formulated with a component that might provide media for bacterial proliferation. The tablet should be formulated to dissolve or erode slowly in the presence of a small volume of serum or fluid, over a 20- to 40-min period, when loosely packed in the extraction site.

Tablets Administered by Other Routes

Implantation Tablets. Implantation or depot tablets are designed for subcutaneous implantation in animals or man. Their purpose is to provide prolonged drug effects, ranging from one month to a year. They are usually designed to provide as constant a drug delivery release rate as possible. These tablets are usually small, cylindric, or rosette-shaped forms, and are typically not more than 8 mm in length. Since there are two major safety problems with this form of drug administration, this class of dosage form has achieved little use in humans. The safety problems include the need for a surgical technique to discontinue therapy, and tissue toxicity problems in the area of the implantation site. A special injector utilizing a hollow needle and plunger (the Kern injector) may be used to administer rod-shaped tablets. Surgical techniques may be required for administering tablets of other shapes. Implantation tablets have been largely replaced by other dosage forms, such as diffusion-controlled silicone tubes filled with drug or biodegradable polymers that contain entrapped drug in a variety of forms. The primary application of current implantation tablets and depot forms is to the administration of growth hormones to food-producing animals. In this case, the implant or depot should be made in an animal structure that is not consumed. The ear of the animal is typically used, and appropriate drug release to the animal from the ear site must be achieved.

Vaginal Tablets. Vaginal tablets or inserts are designed to undergo slow dissolution and drug release in the vaginal cavity. The tablets are typically ovoid or pear-shaped to facilitate retention in the vagina. This tablet form is used to release antibacterial agents, antiseptics, or astringents to treat vaginal infections, or possibly to release steroids for systemic absorption. The tablets are often buffered to promote a pH favorable to the action of a given antiseptic agent. The buffer pH, however, should not be greatly removed from physiologic pH. The vehicle of these tablets is typically a slowly soluble material similar to agents described for the preparation of buccal and sublingual tablets. The tablets should be designed to be compatible with some type of plastic tube inserter, which is usually employed to place the tablet in the upper region of the vaginal tract.

Tablets Used to Prepare Solutions

Effervescent Tablets. Effervescent tablets are designed to produce a solution rapidly with the simultaneous release of carbon dioxide. The tablets are typically prepared by compressing the active ingredients with mixtures of organic acids—such as citric acid or tartaric acid—and sodium bicarbonate. When such a tablet is dropped into a glass of water, a chemical reaction is initiated between the acid and the sodium bicarbonate to form the sodium salt of the acid, and to produce carbon dioxide and water. The reaction is quite rapid and is usually completed within one minute or less. In addition to having the capability of producing clear solutions, such tablets also produce a pleasantly flavored carbonated drink, which assists in masking the taste of certain drugs. For many years, various saline cathartics were prepared as effervescent mixtures and powders. The most widely produced effervescent tablet today is one that contains aspirin. If a clear solution is to be produced, the drug that is incorporated in the tablet must be soluble at a neutral or slightly alkaline pH, and any lubricant or other additive employed to facilitate tablet compression must be water-soluble.

The advantage of the effervescent tablet as a dosage form is that it provides a means of extemporaneously preparing a solution containing an accurate drug dose. As in the case of aspirin, this dosage form may provide other advantages as well. The solution produced by the most widely marketed effervescent aspirin tablet has a pH of about 8. If the volume of the solution and the pH of the solution are adequate to raise the gastric contents to neutral or near-netural pH, the aspirin remains in solution and is rapidly available upon emptying from the stomach. Some literature has been published to indicate that this form of aspirin is less irritating to the stomach mucosa. In addition, neutralization of gastric contents may be rapidly obtained from solutions of this type of tablet. The product does, however, represent a "systemic" antacid effect, with an

appreciable dose of sodium or potassium, and thus does not represent a recommended method of producing routine gastric neutralization.

The disadvantage of the effervescent tablet, and one reason for its somewhat limited utilization, is related to the difficulty of producing a chemically stable product. Even the moisture in the air during product preparation may be adequate to initiate effervescent reactivity. During the course of the reaction, water is liberated from the bicarbonate, which autocatalyzes the reaction. Providing adequate protection of effervescent tablets in the hands of the consumer is another problem. The moisture to which tablets are exposed after opening the container can also result in a rapid loss of product quality in the hands of the consumer. It is for this reason that effervescent tablets are specially packaged in hermetic-type foil pouches or are stack-packed in cylindric tubes with minimal air space. Another reason for such packing is the fact that the tablets are usually compressed to be soft enough to produce an effervescent reaction that is adequately rapid.

A number of investigators have looked at alternative effervescent components in recent years in an attempt to produce a more chemically stable system. Such studies have included investigation of malic acid, fumaric acid, and various acid anyhdrides, in combination with newer carbonate sources such as sodium glycine carbonate and various sesquicarbonates. If, in the future, more chemically stable effervescent mixtures are identified that continue to provide rapid reactivity in water, the effervescent tablet system may expand as a method of producing extemporaneous drug-containing solutions.

Dispensing Tablets (DT). Dispensing tablets are intended to be added to a given volume of water by the pharmacist or the consumer, to produce a solution of a given drug concentration. Materials that have been commonly incorporated in dispensing tablets include mild silver proteinate, bichloride of mercury, merbromin, and quaternary ammonium compounds. The dispensing tablet must typically comprise totally soluble components, and the excipient ingredients of the tablet must not produce deleterious effects in the intended application of the solution or undesirable physical or chemical interactions with the active agent. In some cases, as in applications where the solution is to be used in contact with mucous membranes or on wounds, the tablet may also contain components to provide buffering or isotonicity. Dispensing tablets are less commonly used than formerly, since they cannot be employed on a routine basis with water of known quality to produce sterile solutions. Another difficulty with dispensing tablets is that some of the components previously used in this dosage form are highly toxic and are extremely hazardous, and even lethal, if mistakenly swallowed. Great care must be taken in the packaging and labeling of such tablets to attempt to prevent their oral consumption. In the past, bichloride of mercury was usually prepared in coffin-shaped tablets, with an embossed skull and crossbones to emphasize its toxicity.

Hypodermic tablets (HT). Hypodermic tablets are composed of one or more drugs with other readily water-soluble ingredients and are intended to be added to sterile water or water for injection. Such extemporaneous preparation of an injectable solution was once widely used in medicine, because the physician, especially the rural physician, could carry many vials of such tablets in his bag with only one bottle of sterile water for injection, to prepare a great many types of injectable medications as the need arose. Hypodermic tablets are little used today in this country because their use increases the likelihood of administering a nonsterile solution, even though portable sterile filtration equipment exists to help assure the sterility and freedom from particulate matter in such a product. Furthermore, since physicians today practice most of their medicine from an office or a hospital, the advantage of portability of tablets for injection is far outweighed by the hazards and disadvantages of this dosage form in most medical situations.

Tablet Triturates (TT). Tablet triturates are small, usually cylindric, molded, or compressed tablets. Though rarely used today, they provided an extemporaneous method of preparation by the pharmacist. The drugs employed in such products were usually quite potent and were mixed with lactose and possibly a binder, such as powdered acacia, after which the mixture was moistened to produce a moldable, compactable mass. This mass was forced into the holes of a mold board fabricated from wood or plastic, after which the tablets were ejected using a pegboard, whose pegs matched the holes in the mold. The tablets were then allowed to dry and were available for dispensing. Since virtually every conceivable drug that would be useful in a tablet dosage form is available in that form, or in capsule form, there is virtually no need today for pharmacists to prepare tablets extemporaneously. Since in preparing this form of molded tablet, alcohol was commonly used to wet the powder mass to expedite drying of the tablets, tablet triturates were usually soft and

quite friable. Many of the drugs employed in these tablets were highly potent, and drug migration could occur as the alcohol evaporated, so content uniformity of such tablets was often questionable. Because of these problems and the question of producing bioavailable dosage forms from such extemporaneous preparations, the tablet triturate is rarely seen today.

Future Trends

Formulation and Product Trends

Uncoated Tablets. Future design, formulation, and manufacture of conventional uncoated tablets will follow the existing trend to more efficient processing, combining or eliminating processing steps where possible, reducing handling, reducing processing variables, minimizing production time, and further reducing total production costs. Where possible, direct compression will continue to expand as a preferred method of tablet manufacture, and new and improved excipient materials that are especially compatible with direct compression and extend its utility, reliability, or simplicity as a process will find favor in pharmaceutical solid dosage form development. Where direct compression is not the process of choice, use of high-shear mixer/granulators will continue to expand, followed by efficient and rapid fluid-bed drying of the agglomerates. More progressive companies willoptimize formulations and processing conditions to produce the highest-quality agglomerates (granulations) at the lowest cost, employing regression and other mathematical approaches. Optimizing binder efficiency and processing conditions for reliable production of consistent agglomerates in a single high-shear mixer/granulator will be a major goal in such studies. Automation and computer control will rapidly expand in monitoring and controlling tablet production operations and entire tablet production facilities. Some type of continuous system to monitor tablet weight, utilizing instrumented tablet presses or high-speed electro-balances tied in to press operation, will become routine good manufacturing practice for high-speed tablet production.

Excipient Materials. New and improved excipients will continue to be developed to meet the needs of advancing tablet manufacturing technology. In recent years, new improved disintegrants have been marketed that are extremely efficient in lower concentrations, and that have good compressional properties. New direct compression diluents have also become available, as noted in the previous section on tablet design and formulation. A number of these newer excipient materials are polymeric, such as the cross-linked form of carboxymethylcellulose, which is sold under the trade name Ac-Di-Sol. It is predicted that the majority of the new future excipients will be polymers, based on their ability to produce a wide range of materials and properties according to molecular structural alterations. The majority of these polymer derivatives are of natural origin, based on their better regulatory approval status.

Coatings. Solvent-based film coating will continue to decline, based on high solvent costs and EPA and OSHA restrictions. They will be virtually replaced by completely water-based systems. Polymer solutions in water may be used to produce water-soluble film coatings. Colloidal dispersions of polymers (such as the 30% ethylcellulose dispersion marketed as Aquacoat), which produce dense films by particle coalescence, not only will make the formation of water-soluble film coating a highly efficient process, (virtually equal to earlier solvent-based methods), but will show the way to produce totally water-based enteric and sustained-release coatings. Side-vented coating pans, and pan designs with improved drying efficiencies will virtually replace the conventional solid-pan design. Improved methods of fabricating small spherical drug-containing particles will continue to develop, as will more reproducible methods of coating such particles. Air suspension coating will continue to play a role in coating such small particles; it is not likely that air suspension coating will grow appreciably as a tablet coating method.

Controlled-Release Tablets. Theoretically, tablets offer the lowest-cost approach to sustained- and controlled-release solid dosage forms. Currently, the vast majority of such products are coated pellets placed in capsules. This particulate approach to sustained release has offered several advantages: metered particle emptying from the stomach, utilization of a plurality of coatings, and several release profiles for the various populations of coatings, thereby permitting an immediate release fraction followed by a sustaining fraction. Matrix slow-releasing tablets cannot match these characteristics. For this reason, and based on public expectations (or those of marketing specialists) that controlled-release products are expected to be beads in a capsule, relatively few sustained-release oral products have been in tablet form.

A major recent break in that trend is the highly successful sustained-release theophylline product of Key Pharmaceuticals, Inc., Theo-

Dur. This is a unique type of sustained-release tablet that overcomes some of the limitations of earlier matrix tablets. Under gastric pH conditions, the Theo-Dur tablet slowly erodes; however, at a pH corresponding to the upper small intestine, the tablet disintegrates rapidly to release coated particles, which in turn slowly release drug. Two different release mechanisms are operative, neither of which is zero-order—erosion and decreasing surface area, and dissolution of coated particles—but the overall tablet release profile comprising the two mechanisms in sequence is nearly linear for most of the dose in the tablet. The result is the ability to control theophylline blood levels in a narrow range, above the minimum effective level and below the toxic level. This type of sustained-release tablet has clearly shown the potential of the tablet as a reliable sustained-release dosage form with good release profile precision.[36,37] More sustained-release tablet forms of this type are sure to follow.

A prolonged gastric retention coated tablet system has been reported.[38] The tablet utilizes a cross-linked polymer coating that has the capacity to swell greatly and rapidly in the stomach and be restricted there by physical size. Gastric fluid that penetrates the hydrated swollen film dissolves the drug within the sac enveloping the tablet, and drug is released from solution by diffusion across the hydrated membrane/film. Drug release is at a constant rate so long as the concentration of drug within the sac exceeds the capacity of the membrane to deliver the drug, and the film/membrane is thus providing the rate-limiting step. If the dimension of the fluid-filled sacs exceeds approximately 2 cm, these dosage units consistently remain in the stomach for at least 6 to 8 hours, releasing drug in solution to the gastric contents at a constant rate. This gastric retention tablet dosage form reflects the type of innovation to control not only the rate of drug release, but also the site of release, that will undoubtedly continue in the years ahead to further improve and enhance drug delivery capabilities.

The Oros product of the Alza Corporation is another new zero-order sustained-release tablet product; it is based on osmotic pressure as the rate-controlling process. This concept will also expand the use of tablet dosage forms in controlled release. The first such products are already being marketed in Europe, and the drug indomethacin is about to be marketed in the United States in an Oros system, at the time of this writing.

Film coatings that may be applied to tablets to provide diffusion-controlled "membranes" for constant drug release rate profiles as the tablet dosage form moves along the GI tract are also under active development. Such a system offers the potential ultimate dosage form as a simple, low-cost, and reproducible physicochemical approach to oral controlled and sustained drug release.

Manufacturing Improvements

Basic Improvement Areas. Wet granulation has traditionally been a highly labor-intensive and time-consuming process (see Table 11-3). In the last 20 years, however, significant improvements in tablet manufacturing efficiency have taken place. These can be attributed to four basic areas: the elimination or combination of processing steps, the improvement of specific unit operations, the design of new equipment specifically oriented to granulation objectives, and the improvement of materials handling techniques and systems. Illustrating the use of these improvement areas, Table 11-6 compares the processing steps of Lederle's old tablet-manufacturing process to its new tablet-manufacturing process.

Elimination or Combination of Steps. Tables 11-3 and 11-6 indicate the processing steps that may be omitted on conversion from wet granulation to direct compression. As noted, new mixer/granulators allow several processes of wet granulation to be conducted in rapid succession or to be combined in one piece of equipment.

Unit Operation Improvement. The efficiency of new tablet manufacturing methods, as exemplified by the new process, was achieved by enhancing the efficiency of three specific unit operations. First, material blending was improved by replacing slow-speed planetary type mixers with high-speed mixer/granulators. Second, the tablet compression operation was improved by replacing old single-fill-station, gravity-fed compression machines with newer high-speed, multi-station presses, with induced die feed and automated weight control. Third, the coating operation was brought into better compliance with EPA standards by switching from organic-solvent based systems to aqueous systems, which were further aided by side-vented coating equipment having greatly improved drying efficiencies.

Materials Handling. A major labor-saving change made in equipment designs allowed material to be moved by gravity. A granulation gravity feed system was designed that eliminated the manual feeding of granulation into the presses.

TABLE 11-6. *Unit Processing of Solid Dosage Forms (Tablet Manufacturing)—Lederle Laboratories*

Old Process (Wet Granulation)	*New Process (Direct Compression)*
Raw Materials	Raw materials
Weighing and measuring	Weighing and measuring (automatic weigher and recording system)*
Screening	Gravity feeding
Manual feeding	Blending (Littleford blender)
Blending (slow-speed planetary mixer)	Gravity feeding from the storage tank*
Wetting (hand addition)	Compression (high-speed rotary press)*
Subdivision (comminutor)	Aqueous coating (Hi-Coater)
Drying (fluid bed dryer)	
Subdivision (comminutor)	
Premixing (barrel roller)	
Batching and lubrication (ribbon blender)	
Manual feeding	
Compression (Stokes rotary press)	
Solvent film coating (Wurster column)	
Tablet inspection (manual)	

*In planning phase, to be installed later.
Courtesy of Lederle Laboratories, Pearl River, NY.

With use of similar techniques, even wet granulation operations have been made more efficient, and a hypothetical state-of-the-art processing scheme is presented in the flow chart in Figure 11-19. All processing steps including drying might be combined in a single processor in the wet granulation method of the future. Such equipment will minimize materials handling, labor requirement, and human variables.

Equipment. Various equipment improvements that would combine several of the wet granulation processing steps are being investigated. One such method is the use of the sprayer dryer. The components of the formula-diluent, binder, disintegrant, and lubricant may be suspended and/or dissolved in a suitable vehicle according to their nature. The solids should represent at least 50 to 60% of the suspension. Under constant stirring to maintain good distribution, the slurry is pumped to an atomizing wheel, which whirls the material into a stream of hot air. The heat removes the liquid carrier, and the solids fall to the bottom of the dryer as fine, spherical granules ranging from as low as 10 to as high as 250 microns in diameter, the size depending on the speed of the wheel and the flow rate of the feed. The drug may be mixed with this "base" in proportions as high as 1:1. If

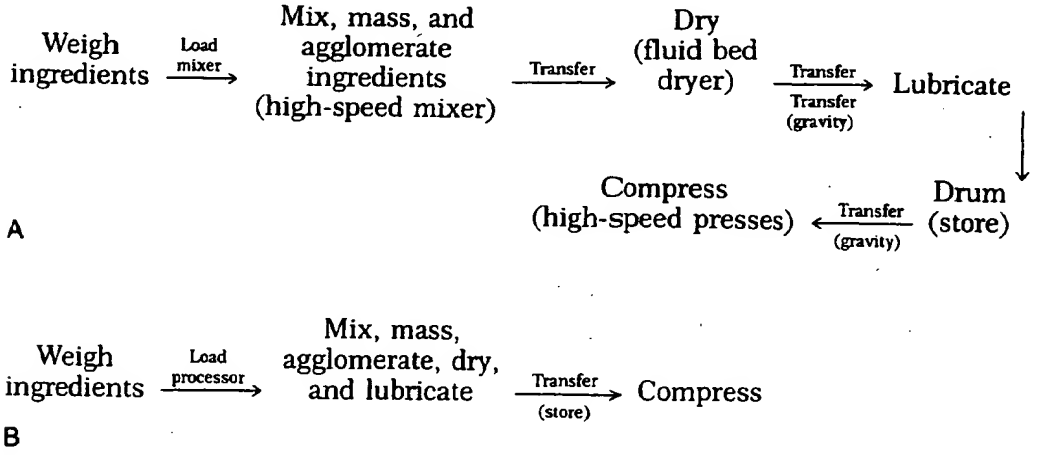

FIG. 11-19. *Flow charts depict state-of-the-art wet granulation processing of the 1980s* (A), *and projected wet granulation processing methods of the future—1990 and beyond* (B). *(Adapted from Anderson, N.R., Banker, G.S., and Peck, G.E.: Principles of improved tablet production system design.* In *Pharmaceutical Dosage Forms: Tablets. Vol. 3. Edited by H. Lieberman and L. Lachman. Marcel Dekker, Inc., New York, 1982, p. 14, by courtesy of Marcel Dekker, Inc.)*

the drug remains stable with the temperatures and solvents used, it may also be included in the slurry.

Fluid Bed Spray Granulators. The first equipment reported in the pharmaceutical literature to provide continuous-batch wet granulation was fluid bed drying equipment, which was modified by the addition of spray nozzles or fluid injectors to provide addition of liquid binding and adhesive agents to dry-powdered materials for powder agglomeration, followed by drying in the same equipment.

Figure 11-20 presents a schematic cross-section of such a fluid bed spray granulator. The airflow necessary for fluidization of these powders is generated by a suction fan mounted in the top portion of the unit, which is directly driven by an electric motor. The air used for fluidization is heated to the desired temperature by an air heater, after first being drawn through prefilters to remove any impurities. The material to be processed is shown in the material container just below the spray inlet. The liquid granulating agent is pumped from its container and is sprayed as a fine mist through a spray head onto the fluidized powder. The wetted particles undergo agglomeration through particle-particle contacts. Exhaust filters are mounted above the product retainer to retain dust and fine particles. After appropriate agglomeration is achieved, the spray operation is discontinued, and the material is dried and discharged from the unit.

The advantages of such rapid wet massing, agglomeration, and drying within one unit are obviously attractive. Excluding equipment cleanup, the process may readily be sequentially completed within 60 to 90 min or less.

There are several difficulties in the fluid bed spray granulating process. Fluid bed systems may not provide adequate mixing of powder components. In fact, there is a tendency for

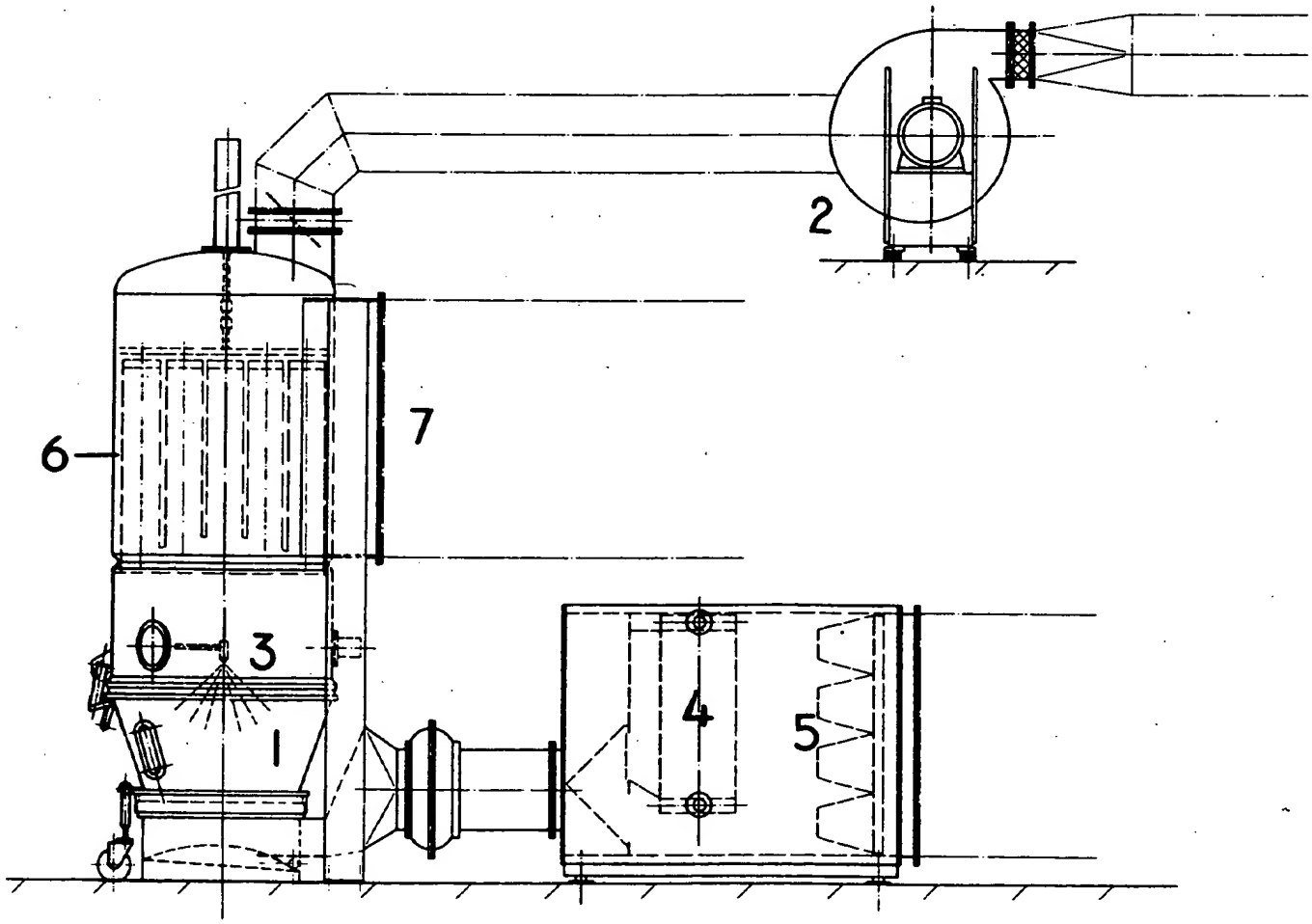

FIG. 11-20. *Schematic diagram of a fluid bed granulator dryer. (1) Material container. (2) Air suction fan. (3) Fluid spray head. (4) Inlet air heater. (5) Inlet air filter. (6) Exhaust air filters. (7) Explosion relief panels. (Courtesy of Aeromatic, Iowaco, NJ.)*

demixing to occur when there are disparities in particle size or density in the materials being processed. Particles with granulating agents on their surfaces tend to stick to the equipment filters, reducing the effective filter surface area, causing product loss, and increasing cleanup difficulties. Special attention is also needed for safety in any fluid bed processor. Dust explosions can occur in a fluid bed dryer, with flammable solvents or with dry materials that develop static charges, and all production size fluid bed equipment must contain explosion relief panels.

Double-Core and Twin-Shell Blenders With Liquid Feed and Vacuum-Drying Capabilities. A number of manufacturers of both double-cone and twin-shell blenders have produced equipment modifications that provide the potential for sequencing the operations of powder mixing, wet massing, agglomeration, and drying. The specialized equipment typically includes a liquid feed through the trunnion of the machine, leading to a spray dispenser located above the axis of rotation of the unit; a vacuum inlet through the same or the opposing trunnion leading to a vacuum intake port covered by a nylon or other appropriate fine-filter sleeve, which is also located above the axis of rotation and out of the direct path of powder motion; and agitating elements capable of rotation within the powder mass contained in the blender. The blender may also employ a double-wall construction to provide circulation of a heating medium; in other cases, the systems are designed to operate at room temperature and use vacuum as the sole source of water or liquid removal.

Figure 11-21 provides a cutaway view of a double-cone mixer-dryer processor. As in any vacuum-drying operation, equipment and drying costs are relatively high. Drying times are considerably longer than with the fluid bed granulator processor. The double-cone or twin-shell processor would be considerably easier to clean, however. The attractiveness today of the double-cone or twin-shell mixer, granulator, and dryer as a continuous-batch processor of wet granulation products hinges on the use of nonaqueous granulating liquids. Standard auxiliary equipment is available to condense solvent vapors and provide substantially complete solvent recovery. This is important from two standpoints: solvent vapors are not discharged to the atmosphere, an environmental consideration, and efficient solvent recovery is achievable, an economic consideration.

Day-Nauta Mixer-Processor. The Nauta mixer is a vertical screw mixer (Fig. 11-22). A screw assembly is mounted in a conical chamber, with the screw lifting the powder to be blended from the bottom to the top. The screw assembly orbits around the conical chamber wall to ensure more uniform mixing. The Nauta mixer was originally designed not as a wet gran-

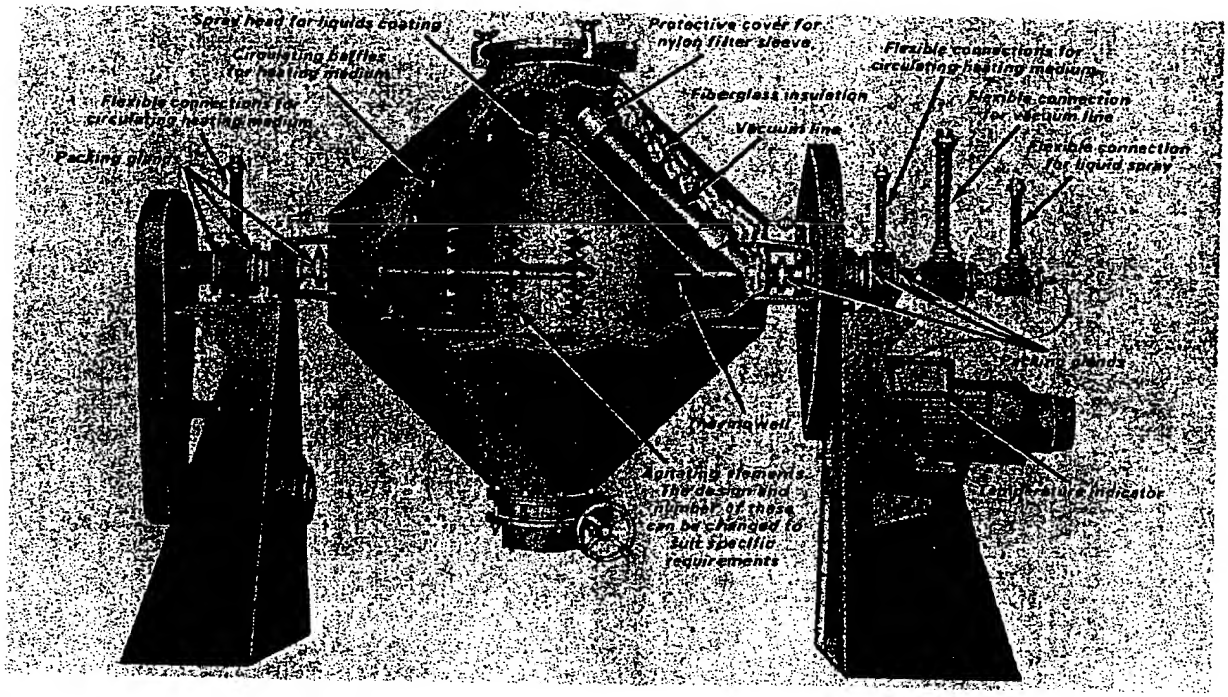

FIG. 11-21. *A cutaway view of a double-cone mixer-dryer processor. (Courtesy of Paul O. Abbe, Little Falls, NJ.)*

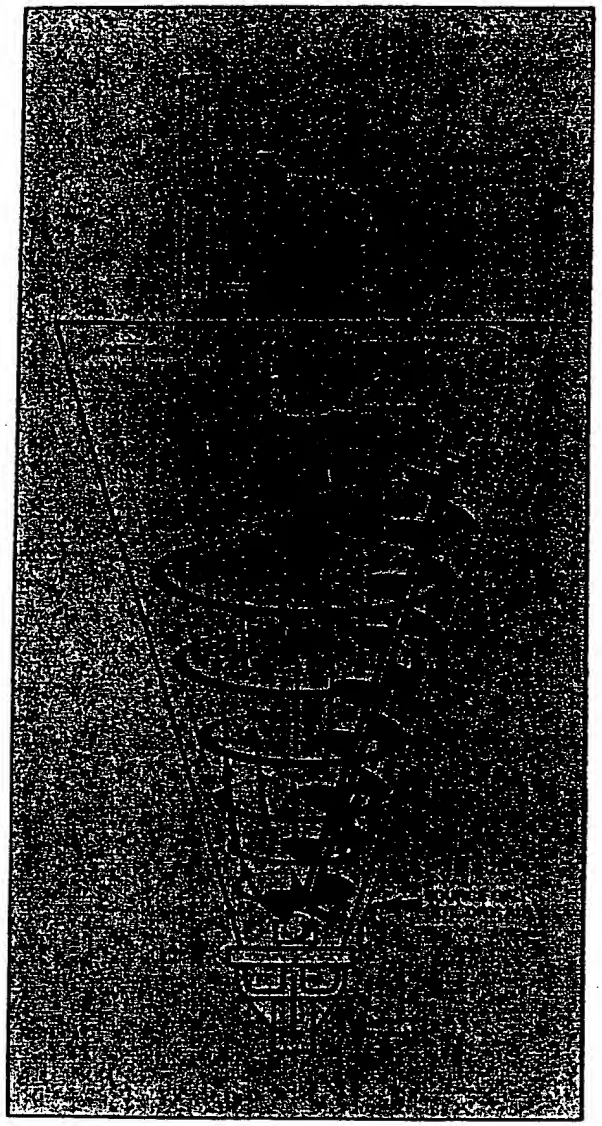

FIG. 11-22. *Schematic diagram of the Nauta processor. (1) Screw assembly. (2) Conical chamber. (3) Source of hot, dry air. Hot air moves up through the material (vertical arrows), which is kept in motion by the orbiting screw assembly (circular arrows). (Courtesy of Day Mixing, Cincinnati, OH.)*

ulation mixer-granulator but as a powder and semisolids mixer. The basic operation following power mixing includes incorporation of the liquid-granulating agent, wet massing, and drying as hot, dry air is passed through the wet material. The hot air moves up through the material, which is kept in a state of motion by the orbiting screw assembly. It dries the granulation and exits the top of the processor. If additional help is required for particular drying needs, the Nauta can be constructed to utilize vacuum drying. Accessory equipment designed to monitor and control processor operation includes a lump breaker, which may be attached at the bottom of the conical chamber; a temperature monitor; a nuclear, noncontact density gauge; an ammeter or wattmeter; an infrared moisture analyzer; and a sampling system.

Topo Granulator. The Topo granulator was developed in Austria for the preparation of granules and coated particles under high vacuum. The machine is illustrated in Figure 11-23. The material to be granulated or coated is placed in the chamber, which may be accomplished by dust-free suction. A granulating compartment is then loaded by vacuum, and each granulating fluid or addition product (liquid or solid) is added as desired by imploding the added ingredient(s) upon the components already in the chamber. When granulating agents are thus added to the chamber under vacuum, the granulation forces are reportedly greatly increased to produce the necessary compaction. The resultant agglomerated particles can then be dried under vacuum in the chamber. Some of the advantages reported for this granulation process are a reduction in the required volume of granulating fluid; a unique agglomeration mechanism

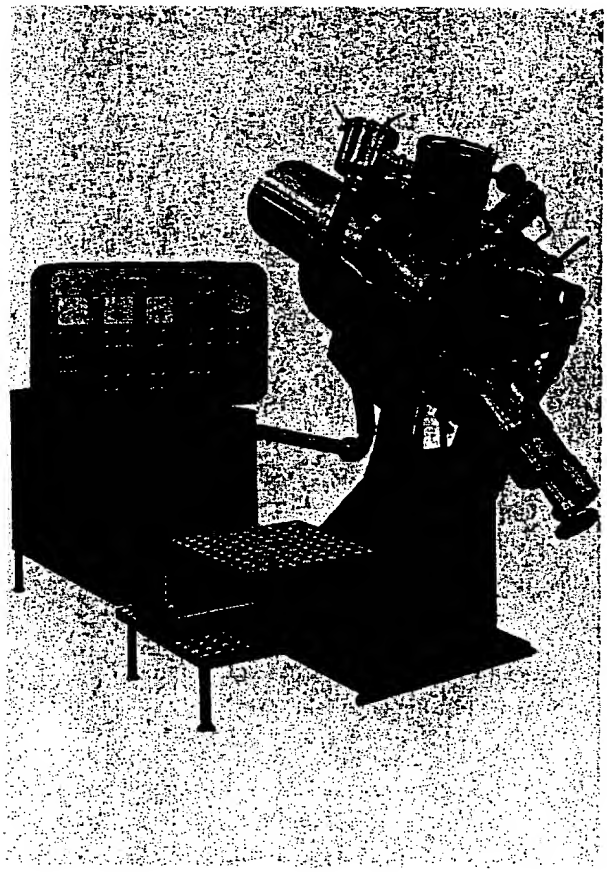

FIG. 11-23. *The Topo granulator. (Courtesy of Machines Collette, Wheeling, IL.)*

for the granulation process as it occurs under vacuum; a reduction in the amount of excipient materials that may be required to produce a satisfactory granule, owing to the intensified compaction of the granulation process; and generation of a granulation that produces tablets of exceptional hardness and stability.

By imploding coating materials on existing granulations, coating within the unit is reportedly possible. It has also been reported that by alternately imploding various drug and excipient materials, the equipment is capable of effectively separating incompatible drugs or of producing effervescent products of improved stability to moisture. Unfortunately, little published scientific or technical information is available regarding products produced by this equipment.

CF Granulator. The CF granulator utilizes a cylindric bowl with a rotating base plate (Fig. 11-24). Passing through the space between the bowl and base plate is fluidizing and drying air. A feeding device feeds powders, granules, or other solids into the machine. The rotating base and air form the material into rounded particles, a doughnut-like ring along the wall of the chamber, in a twisted-rope motion. While the material is thus formed, binding or coating solutions and powders can be sprayed onto the material. Operating in this fashion, materials can be granulated, agglomerated or coated, and dried within a reasonably limited time. The equipment is also used to produce spherical beads of drug applied to sugar beads, which may then be coated in the equipment for controlled-release purposes.

Computer Process Control. As the tablet manufacturing processes continue to be improved in the four areas indicated, human worker involvement will continue to decline. As human involvement requirements are reduced, computer control of the process is inevitable. There are many good reasons for implementing computer process control.

Rigid control enforcement
Operational information
Documentation of the process
Security of the process and its control
Increased consistency
Increased flexibility
Increased reliability
Increased productivity

Merck, Sharp and Dohme's computer-controlled Aldomet plant has shown that tablet production under computer control with limited human intervention is possible in a continuous mode.

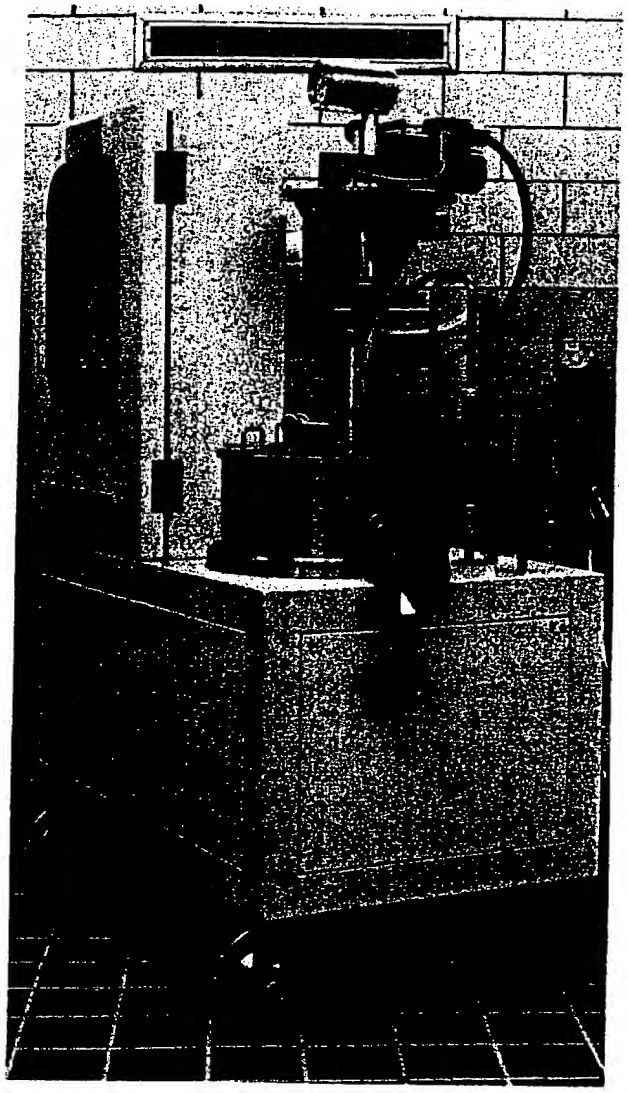

FIG. 11-24. *The CF granulator. (Courtesy of Vector Corporation, Marion, IA.)*

In the common batch mode of tablet production, individual unit operations such as coating processes, fluid bed dryers and tablet press monitors are becoming automated by microcomputers. There are obstacles to computer control, including the need for smaller and more powerful computer devices, better process interfacing sensors, particularly of the "composition" type, and better man/machine interfacing. Therefore, as the price and size of computers continue to decrease, as the availability of sensors increases, and as our knowledge of tablet processes increases, the computer control of tablet batch operations will rapidly grow in the future.

Appendices

Appendix A

Common Tablet Ingredients in Wet Granulation Formulas

Phenobarbital Tablets

Ingredient	*Quantity per Tablet*	*Quantity per 10,000 Tablets*
Phenobarbital	65 mg	650 g
Lactose (fine powder)	40 mg	400 g
Starch (paste)	4 mg	40 g
Starch (dry)	10 mg	100 g
Talc	10 mg	100 g
Mineral oil, 50 cps	4 mg	40 g

Mix the phenobarbital and lactose, and moisten with 10% starch paste to proper wetness. Granulate by passing through a 14-mesh screen, and dry at 140°F. When dry, pass through a 20-mesh screen; add the dry starch and talc; mix well. Finally, add the mineral oil, mix again, and compress using $^{9}/_{32}$-in. standard cup punches.

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Aminophylline Tablets

Ingredient	*Quantity per Tablet*	*Quantity per 10,000 Tablets*
Aminophylline	100 mg	1.0 kg
Tricalcium phosphate	50 mg	0.5 kg
Pregelatinized starch	15 mg	0.15 kg
Water	q.s.	q.s.
Talc	30 mg	0.3 kg
Mineral oil, light	2 mg	0.02 kg

Mix the aminophylline, tricalcium phosphate, and starch; moisten with water. Pass through a 12-mesh screen, and dry at 100°F. Size the dry granules through a 20-mesh screen; add the talc and mix. Add the mineral oil, mix for 10 min, and compress using $^{5}/_{16}$-in. deep cup punches for enteric coating.

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Chewable Antacid Tablets

Ingredient	*Quantity per Tablet*	*Quantity per 10,000 Tablets*
Aluminum hydroxide (dried gel)	400 mg	4.0 kg
Magnesium hydroxide (fine powder)	80 mg	0.8 kg
Sucrose (confectioner's)	20 mg	0.2 kg
Mannitol (fine powder)	180 mg	1.8 kg
Polyvinylpyrrolidone (10% solution)	30 mg	0.3 kg

Mix the first four ingredients, and moisten with a 10% PVP solution in 50% ethanol. Granulate by passing through a 14-mesh screen. Dry at 140 to 150°F. Size through a 20-mesh screen, add the oil of peppermint mixed with the Cab-O-Sil and finally the magnesium stearate; mix well and compress using ½-in. flat-face beveled-edge punches.

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Chewable Laxative Tablets

Ingredient	*Quantity per Tablet*	*Quantity per 10,000 Tablets*
Phenolphthalein	64 mg	0.64 kg
Powdered sugar	750 mg	7.5 kg
Powdered cocoa (defatted)	350 mg	3.5 kg
Gelatin (10% solution)	q.s.	q.s.
Calcium stearate	12 mg	0.12 kg
Talc	60 mg	0.60 kg

Mix the phenolphthalein, sugar, and cocoa, and moisten with the gelatin solution. Pass through an 8-mesh screen, and dry in a tray oven at 120 to 130°F. When dry, reduce granule size by passing through a 16-mesh screen. Mix the calcium stearate and talc, pass through a 100-mesh screen, add to the granulation, and compress to weight using $^{5}/_{8}$-in. flat-face punches.

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Ferrous Sulfate Tablets

Ingredient	*Quantity per Tablet*	*Quantity per 10,000 Tablets*
Ferrous sulfate (dried)	300 mg	3.0 kg
Corn starch	60 mg	0.60 kg
20% Sugar solution	q.s.	q.s.
Explotab	45 mg	0.45 kg
Talc	30 mg	0.30 kg
Magnesium stearate	4 mg	0.04 kg

Mix the ferrous sulfate and cornstarch; moisten with sugar syrup to granulate through a 12-mesh screen. Dry in a tray oven overnight at 140 to 150°F. Size through an 18-mesh screen; add the Explotab, talc, and magnesium stearate, and compress to weight using $^{3}/_{8}$-in. deep cup punches in preparation for sugar-coating.

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Appendix B

Common Tablet Ingredients in Dry Granulation Formulas

Aspirin Tablets (5-Grain)

Ingredient	*Quantity per Tablet*	*Quantity per 10,000 Tablets*
Aspirin (20-mesh)	325.0 mg	3.250 kg
Starch USP (dried	32.5 mg	0.325 kg
Cab-O-Sil	0.1 mg	0.010 kg

Combine the aspirin, starch, and Cab-O-Sil, and mix in a P-K twin-shell blender for 10 min. Compress into slugs using 1-in. flat-face punches. Reduce the slugs to granulation by passing through a 16-mesh screen in a Stokes Oscillating Granulator or through a Fitzpatrick Mill with a #2B screen, at medium speed, and with knives forward. Transfer the granulation to a tablet machine hopper, and compress into tablets using $^{13}/_{32}$-in. standard concave punches.

Note: All operations should be carried out in a dehumidified area at a relative humidity of less than 30% at 70°F.

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Effervescent Aspirin Tablets (5-Grain)

Ingredient	*Quantity per Tablet*	*Quantity per 10,000 Tablets*
Sodium bicarbonate (fine granular)	2.050 g	20.500 kg
Citric acid (fine granular)	0.520 g	5.200 kg
Fumaric acid (fine granular)	0.305 g	3.050 kg
Aspirin (20-mesh, granular)	0.325 g	3.250 kg

Mix the above ingredients in a P-K twin-shell blender for 20 min; transfer to a tablet machine equipped with 1¼-in. flat-face punches, and compress slugs to approximately ⅜-in. thick. Grind the slugs through a 16-mesh screen. Mix for 5 min in a twin-shell blender, and compress into tablets using ⅞-in. flat-face beveled-edge punches.

Note: All operations should be carried out in a dehumidified area at a relative humidity of less than 30% at 70°F.

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Appendix C

Common Tablet Ingredients in Direct Compression Formulas

Acetaminophen Tablets (USP)

Ingredient	*Quantity per Tablet*	*Quantity per 10,000 Tablets*
Acetaminohpen USP (granular or large crystal)*	325.00 mg	3.25 kg
Avicel PH 101	138.35 mg	1.3835 kg
Stearic acid (fine powder)	1.65 mg	0.0165 kg

*If smaller crystalline size acetaminophen is desired to improve dissolution, it is necessary to use a higher proportion of Avicel, to use PH 102 in place of PH 101, and to use a glidant. All lubricants should be screened before being added to blender.

Blend the acetaminophen and Avicel PH 101 for 25 min. Screen in the stearic acid, and blend for an additional 5 min. Compress tablets using $^{7}/_{16}$-in. standard concave or flat beveled tooling.

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Vitamin B_1 Tablets (Thiamine Hydrochloride USP; 100 mg)

Ingredient	*Quantity per Tablet*	*Quantity per 10,000 Tablets*
Thiamine hydrochloride USP	100.00 mg	1.0 kg
Avicel PH 102	83.35 mg	0.8335 kg
Lactose (anhydrous)	141.65 mg	1.4165 kg
Magnesium stearate	6.65 mg	0.0665 kg
Cab-O-Sil	1.65 mg	0.0165 kg

Blend all ingredients except the magnesium stearate for 25 min. Screen in the magnesium stearate and blend for an additional 5 min. Compress using $^{13}/_{32}$-in. standard concave tooling.

Note: Anhydrous lactose could be replaced with Fast Flo lactose with no loss in tablet quality. This would reduce the need for a glidant (which is probably present in too high a concentration in most of these formulations). Usually, only 0.25% is necessary to optimize fluidity.

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Chlorpromazine Tablets USP (100 mg)

Ingredient	*Quantity per Tablet*	*Quantity per 10,000 Tablets*
Chlorpromazine hydrochloride USP	100.00 mg	1.0 kg
Avicel PH 102	125.00 mg	1.25 kg
Dicalcium phosphate (unmilled) or Emcompress	125.00 mg	1.25 kg
Cab-O-Sil	1.74 mg	0.0174 kg
Magnesium stearate	5.25 mg	0.0525 kg

Blend all ingredients except the magnesium stearate for 25 min. Screen in the magnesium stearate, and blend for an additional 5 min. Compress into tablets using 1½₂-in. tooling.

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